EXHIBIT 31

Expert Report of James R. Olson, Ph.D.

City of Spokane v.
Monsanto Company, et al.

Submitted by James R. Olson, Ph.D.
October 11, 2019

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REPORT OF JAMES R. OLSON

My name is James R. Olson. I am currently employed at the University at Buffalo (SUNY Buffalo), where I hold the titles of UB Distinguished Professor, Dept. Pharmacology and Toxicology, Jacobs School of Medicine and Biomedical Sciences and Director, Environmental Health Sciences Division, Dept. Epidemiology and Environmental Health, School of Public Health and Health Professions. My responsibilities in these capacities include both teaching and research. Further information regarding my academic activities is included in a copy of my curriculum vitae, which is attached to this report.

This report will focus primarily on the toxicology and human health effects of exposure to polychlorinated biphenyls (PCBs). These opinions are subject to revisions and supplementation as further information is received in the course of this case.

Since 1978, when I received my Ph.D. from the Medical College of Wisconsin in the combined area of pharmacology and toxicology, my research has concentrated on the pharmacokinetics and toxicology of 2,3,7,8-tetrachlorodibenzo-p-dioxin ("TCDD"; "dioxin") and related compounds including, but not limited to, polychlorinated biphenyls, polychlorinated dibenzo-p-dioxins, and polychlorinated dibenzofurans ("PCBs", "PCDDs", and "PCDFs"). In recognition of my specialized expertise on the subject of the pharmacokinetics and toxicology of TCDD, PCBs, PCDDs, and PCDFs, I have been asked to serve as a special consultant for several U.S. Environmental Protection Agency (EPA) and U.S. Public Health Service (PHS) projects bearing on this subject, including contributing as an author and/or member of the peer review panel for:

- U.S. EPA 1984. Ambient Water Quality Criteria for 2,3,7,8-TCDD (EPA-440/5-84-007). Contributing Author.
- U.S. EPA 1985. Health Assessment Document for Polychlorinated Dibenzo-p-dioxins (EPA-600/8-84-014F). Contributing Author.
- U.S. EPA 1989. Drinking Water Criteria Document for Polychlorinated Biphenyls (PCBs) (NTIS no. PB89-192256). Contributing Author.
- Member of peer review panel for "Toxicological Profile for Selected PCBs (Aroclor-1260, -1254, -1248. -1242, -1232, -1221, and 1016)" The Agency for Toxic Substances and Disease Registry (ATSDR), U.S. Public Health Service, 1987.
- Member of peer review panel for "Toxicological Profile for Chlorinated Dibenzo-p-dioxins" The Agency for Toxic Substances and Disease Registry (ATSDR) 1992, 1994, 1997, 1998.
- Member of peer review panel for "Technical Review Workshop on the Reference Dose (RfD) for Aroclor 1016" U.S. EPA, 1994.
- U.S. EPA September 2000 Draft Final. Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and Related Compounds. Part II: Health

Assessment for 2,3,7,8-TCDD and Related Compounds. Author for Chapter 1, Disposition and Pharmacokinetics (EPA/600/P-00/001Be)

- ATSDR, November, 2000. Toxicological Profile for Polychlorinated Biphenyls (PCBs). Contributing Author for Toxicokinetics and Mechanisms of Action Chapters.

Compensation

I am being compensated at the following rates: $300 per hour for all work done from my home office; $750 per hour for deposition testimony; $3,000 per day for consulting or trial work done out of town, in addition to $300 per hour for oral testimony.

Testimony in the previous 4 years

2016: *Adinolfe, et al. V. United Technologies Corp., d/b/a Pratt & Whitney*, United States District Court Southern District of Florida, West Palm Beach Division

2016: *Town of Westport and Westport Community Schools v. Monsanto Company, et al., United States District Court of Massachusetts*

2017: *City of Hartford v. Monsanto Company, et al*., United States District Court of Connecticut

2019: City of San Diego, et al. V. Monsanto Company, et al., United States District Court, Southern District of California

Opinions

1. Polychlorinated biphenyls (PCBs) pose a significant threat to human health due to their wide-spread use, persistence, and inherent toxicity.

2. It is clear from the published scientific literature that the scientific community knew as early as the 1930s that PCBs produce systemic toxicity in humans and in laboratory animals.

3. Peer reviewed experimental studies conducted during the 1930s through the 1960s did not identify a dose or exposure to PCBs that was safe or without toxicity.

4. PCBs cause an increased risk of a number of adverse health effects, including cancer, developmental effects, diabetes, liver injury, immune system dysfunction, neurobehavioral effects, impaired thyroid function, reproductive system impairment, cardiovascular disease, and chloracne.

5. These adverse health effects are observed in association with PCB exposures in the general population at background, environmental levels of exposure to PCBs.

6. An increase in human exposure to PCBs results in an increased risk of developing cancer and other adverse health effects.

7. PCB exposure to sensitive populations, including children, women of childbearing age, and pregnant women, is especially dangerous due to PCBs adverse developmental effects.

These opinions are based on an extensive review of peer reviewed experimental animal studies and observational epidemiological studies of human populations and consistent, statistically significant associations between PCBs and adverse health effects.

I. BACKGROUND ON PCB PROPERTIES, PRODUCTION, AND FATE

PCBs are very stable and resistant to environmental and biological degradation, thus persist in the environment, wildlife and humans for many years. Due to their extreme stability and lipophilic properties, PCBs and related compounds bioaccumulate and are biomagnified in the food-chain and ultimately expose humans that ingest food products contaminated with PCBs. In addition, humans are exposed to PCBs and related compounds from a wide range of environmental, occupational, and domestic sources through the inhalation, oral, and dermal routes. Adverse health effects associated with exposure to PCBs in humans and laboratory animals include, but are not limited to, cancer, developmental effects, diabetes, liver injury, immune system dysfunction, neurological and neurobehavioral effects, impaired thyroid function, reproductive system impairment, cardiovascular disease, and chloracne (ATSDR 2000; ATSDR 2011; EPA 1985; EPA 1989; EPA 2018; IARC 2016).

Polychlorinated biphenyls (PCBs) are a class of aromatic, chlorinated hydrocarbon with from one to ten chlorines at various positions on the biphenyl ring structure (empirical formula $C_{12}H_{10-n}Cl_n$; n= 1-10), which in theory allows for the formation of 209 different individual PCB congeners. The term "congener" refers to any one particular member of the same chemical family; for example, there are 209 different individual PCB congeners. Each different congener is a different "PCB" and possesses unique chemical, physical and biological properties. The characteristics of individual PCBs vary depending on the number and the position of chlorines on the biphenyl molecule. In general, PCBs have low water solubility and volatility, however, those congeners containing fewer chlorines are more water soluble and more volatile than those with more chlorines.

PCBs were initially introduced into industrial production in 1929 by Swann Chemical. Monsanto Company bought Swann in 1935 and continued producing PCBs for commercial use until 1977 (Brinkman et al., 1980; ATSDR 2000; ATSDR 2011; EPA 1985; EPA 1989; EPA 2018; IARC 2016). The chemical stability, low volatility, non-flammability, high dielectric constant, and compatibility with chlorinated hydrocarbons resulted in many industrial applications for the PCBs, including use as nonflammable hydraulic and lubricating fluids, heat-exchanger and dielectric fluids, plasticizers for plastics and coatings, extenders for pesticides, and as an ingredient of caulking compounds, adhesives, paints, printing inks, and carbonless duplicating paper.

Monsanto manufactured mixtures of individual PCB congeners for commercial use that contained various average percentages of chlorine by weight, while still containing a range of both high and low chlorinated congeners. For example, Monsanto's Aroclor 1254 is a complex mixture of biphenyl congeners containing from one to nine chlorines and has an average chlorine content of approximately 54%. Although Aroclor 1254 is a relatively highly chlorinated PCB mixture, it contains low chlorinated congeners as well as other highly chlorinated congeners. The low chlorinated congeners are more water soluble and volatile than the higher chlorinated congeners. Thus, even highly chlorinated PCB mixtures, like Aroclor 1254, contain lower chlorinated PCBs that more readily volatize into the surrounding environment than the higher chlorinated congeners (Hansen 1999; U.S. EPA 2018; IARC 2016). Once released into the environment, the compositions of commercial PCB mixtures are altered through processes such as volatilization and other kinds of partitioning, chemical and biological transformation, and preferential bioaccumulation of selected congeners. (Hansen 1999; U.S. EPA 2018). Thus, the composition of

PCB mixtures changes following their release into the environment. The types of PCBs that bioaccumulate in fish and other animals and bind to sediments are often the most carcinogenic components of PCB mixtures. As a result, people who ingest PCB-contaminated fish or other animal products and contact PCB-contaminated sediment may be exposed to PCB mixtures that are more toxic than the commercial PCB mixtures contacted by workers and released into the environment (EPA 1996b, 2018).

The general population is exposed to PCBs through the oral, inhalation, and dermal routes, with the ingestion of PCB contaminated food representing the primary source of exposure. After intake, PCBs are distributed throughout the body and stored in most organs and tissues. Due to their profound environmental and biological stability and lipophilicity (high affinity for fat), PCBs bioaccumulate and biomagnify in food chains and are retained in human tissues for the lifetime of an individual.

The biological half-life in humans reflects the time required to remove or excrete half of the chemical body burden by metabolic and non-metabolic pathways. Because of the limited capacity to metabolize and excrete PCBs from the body, the compounds have half-lives spanning years to even over a decade. The biological half-life (t ½) of PCBs is dependent on the specific congeners under investigation. The half-life of the higher chlorinated and more abundant congeners in humans is estimated to be from 9.3 to 15.5 years for PCBs 118 (2,3',4,4',5-penta-CB), 138 (2,2′,3,4,4′,5′-hexa-CB), 153 (2,2',4,4',5,5'- hexa-CB), 170 (2,2',3,3',4,4',5-hepta-CB), and 180 (2,2′,3,4,4′,5,5′-hepta-CB) (Ritter et al., 2011). Lower chlorinated congeners, such as PCB 28 (2,4,4'-tri-CB) and PCB 52 (2,2',5,5'-tetra-CB) have estimated half-lives of 5.6 and 2.6 years, respectively (Ritter et al., 2011). Thus, PCB are exceptionally persistent in humans and are retained in human tissues for decades following a single exposure.

Importantly, humans continue to be exposed to environmental, background levels of PCBs each day, resulting in the long-term bioaccumulation of PCBs, which remain in the body over the lifetime of an individual. The greater the levels of PCBs in the body, the greater risk of developing cancer and other adverse health effects. Therefore, PCBs are of significant concern to human health because of their persistence in the body and their potential to produce a wide range of toxicological responses.

II. EARLY KNOWLEDGE OF PCB TOXICITY

A. PCBs Were Known to Cause Adverse Health Effects as Early as the 1930s and 1940s.

PCBs have been known to have toxic effects for well over half a century. There were a number of reports as early as the 1930s and 1940s in published medical/ scientific journals on the toxic effects of PCBs. Studies in occupationally exposed workers and experimental studies in laboratory animals reported that exposure to PCBs can result in liver injury, a skin lesion known as chloracne, and systemic toxicity. These studies showed that humans may be exposed to PCBs through inhalation of PCB-contaminated air, ingestion of PCB contaminated food and water, and dermal absorption by touching PCB-containing or PCB-contaminated materials. It is also highly relevant that these early studies identified volatilization of PCBs and the resulting inhalation of PCBs as a significant route for human exposure in manufacturing facilities.

Jones and Alden (1936) are physicians from Atlanta that investigated an outbreak of acneform eruption occurring in a group of workers engaged in the manufacture of PCBs (then called chlorinated diphenyls). Within a period from late summer of 1932 to October 1933, 23 out of 24 men working in the manufacture of chlorinated diphenyl were reported to have acneform eruption on the face and body. This article by Jones and Alden was published in 1936 in the Archives of Dermatology and Syphilology.

In 1936, Schwartz published a scientific article in the American Journal of Public Health, which reported on workers engaged in chlorinating the diphenyl in the production of crude Aroclor. The workers were affected with an acne-like condition of the skin and symptoms of systemic poisoning which occurred among workers inhaling fumes from this operation. "Those working with the chlorodiphenyls have complained of digestive disturbances, burning of the eyes, impotence and hematuria." Schwartz (1936) recommended that "there should be periodic medical examination of workers to detect cases of dermatitis and workers in chlorinated naphthalenes and diphenyls should be periodically examined for symptoms of systemic poisoning."

Follicular hyperkeratosis is an important feature of the occupational disease known as chloracne, which is characterized by the appearance of papules, comedones, and cysts. Early clinical reports of chloracne have been reported following occupational exposure to PCBs (Schwartz, 1936; Jones and Alden, 1936; Drinker et al., 1937; Jones, 1941). Epithelial and follicular hyperplasia and hyperkeratosis were also found after application of PCBs on the skin of rabbits (Adams et al, 1941). These authors conclude that the skin of the rabbit is a useful experimental animal model for studying the pathology of chloracne which is observed in humans.

By the mid-1930s, PCBs had created a public health problem sufficient in size to attract the attention of academic researchers, the U.S. Public Health Service, Monsanto, and several large industrial users of PCBs. The Harvard School of Public Health hosted a one-day meeting on June 30, 1937, on the problem of systemic effects of certain chlorinated hydrocarbons including chlorinated diphenyls (Bennett et al., 1938; Montague, 1993). The meeting was attended by representatives from Monsanto, General Electric, the U.S. Public Health Service, the Halowax Corporation, and others (Montague, 1993). During the spring of 1936, Drs. Bennett, Drinker and Warren from Harvard University were informed regarding three fatal cases of jaundice in workmen using chlorinated naphthalenes and chlorinated diphenyls. At the request of the manufacturers of these compounds, these investigators undertook an investigation to determine what systemic effects would result from the administration of these compounds to experimental animals. Three papers were read by these Harvard investigators at the 1937 symposium on chlorinated hydrocarbons, including PCBs, which were later published as three scientific articles in the Journal of Industrial Hygiene and Toxicology (Drinker et al., 1937; Bennett et al., 1938; Drinker 1939).

Drinker et al. (1937) conducted inhalation exposures of rats to chlorinated diphenyl (65 % chlorine content) at an average air concentration of 0.57 mg/ cubic meter. Liver abnormalities included slight to moderate swelling of liver cells, an increase granularity, many mitotic figures and hyalinization, a condition in which normal tissue deteriorates into a homogeneous, translucent material. "Hyalinization was always present as a result of inhalation of chlorinated diphenyl." In the second in the series of 3 published reports, Bennett et al., 1938, stated, "of the various chlorinated hydrocarbons tested, chlorinated dipheyl gave evidence of being the most toxic." The most striking change was the hyalinization of the cell cytoplasm, which remained essentially

unchanged after a 2 month recovery period following inhalation exposure to PCBs (65% chlorine; average air concentrations 0.57 to 0.93 mg/ cubic meter). The authors go on to conclude that "this type of liver injury is persistent and only slowly recovered from." Bennett et al., 1938 goes on to describe this liver injury as degenerative in nature. "The successive degenerative changes were cloudy swelling, fatty infiltration and degeneration and finally, the complete disintegration of the cell." Feeding PCBs to rats produced lethality and at lower doses produced liver injury similar to that observed with inhalation exposure (Bennett et al., 1938).

Drinker et al. (1937) also discussed plans to complete additional testing with a chlorinated diphenyl containing 55% chlorine content, to compare the systemic toxicity with that reported for the chlorinated diphenyl with a 65% chlorine content. Table 1 in Drinker (1939) states permissible limits for the concentrations of various chlorinated hydrocarbons in the air of workrooms based on the systemic toxicity observed in rats following inhalation exposure to these agents. A permissible limit of 0.5 mg/ cubic meter was proposed for chlorinated diphenyl with a chlorine content of 50 – 55% based on inhalation tests conducted in rats. Drinker (1939) also suggested a permissible limit of 10 mg/ cubic meter for chlorinated diphenyl with a chlorine content of 68%, which exhibited less relative systemic toxicity. This observation led Drinker to inquire about the diphenyl with 65% chlorine content used in earlier studies, which he later found may have been a mixture of chlorinated diphenyl and chlorinated diphenyl benzene. Together, the three scientific articles published in the Journal of Industrial Hygiene and Toxicology (Drinker et al., 1937; Bennett et al., 1938; Drinker 1939) consistently reported systemic toxicity, consisting of liver injury, in rats following inhalation exposure to PCBs, and proposed a permissible limit of 0.5 mg/ cubic meter for air in the workroom for chlorinated diphenyl with a chlorine content of 50 – 55% based on inhalation tests conducted in rats. Drinker (1939). However, at no point did the authors report a level of exposure to PCBs that was without toxicity in these experimental studies.

Von Wedel et al. (1943) published a scientific article describing the toxic effects resulting from exposures to chlorinated diphenyls (trade name Aroclor) and chlorinated naphthalenes (trade name Halowax). The authors reviewed the pathological changes found in the skin and liver of workers exposed to these agents, including the death of several workers, which lead them to undertake experimental studies assessing systemic effects that resulted from administration of each of these substances to white mice, guinea pigs and rabbits by inhalation, ingestion and by surface application of the stances to the skin. The experimental results lead to the conclusion that the degenerative effects in the liver are essentially identical regardless of whether the toxic substances were administer by inhalation, ingestion or skin absorption. The authors also suggested a number of steps that could be taken to safeguard workers from exposure to these agents, including protection from skin absorption of these chemicals.

In 1944, J.W. Miller from the U.S. Public Health Service, published a scientific journal article in U.S. Public Health Reports on pathologic changes in animals exposed to a commercial chlorinated diphenyl mixture with an approximate chlorine content of 42% (also known as Aroclor 1242). Guinea pigs, rats and rabbits were exposed to this agent by subcutaneous injections, feeding, and applications to the skin (Miller, 1944). Guinea pigs were very sensitive to PCBs, with a single subcutaneous injection of 69 mg producing skin lesions that were "essentially those of chloracne" and liver damage consisting of fat droplets (fatty liver), central atrophy, basophilic granulation, and focal necrosis. In another experiment with guinea pigs, a single administration of PCBs produced lethality within 13 days in all 10 animals given a single subcutaneous injection

of 345 mg. Observations also suggested that PCBs are relatively easily absorbed through the skin. Thus humans may be exposed to PCBs through inhaling PCB contaminated air, ingesting PCB contaminated food and water, and touching PCB containing materials.

Miller (1944) found that systemic toxicity in all three species was more severe at high doses, at more prolonged duration of exposure and at later time points following exposures to Aroclor 1242. He also reported that the liver of PCB exposed rats contained hyaline bodies, confirming the degenerative response observed in the liver of exposed rats earlier by Bennett et al., 1938. Furthermore, Miller (1944) reports that the chlorinated diphenyl "produced liver changes in the rat having marked differences from those resulting from other toxic substances and that such changes were not found in the guinea pig and rabbit." However, he also reports that, "Most liver damage was found in the guinea pig, less in the rabbit, and least in the rat. This same species order was followed, regardless of dose, duration of test, or mode of administration." These observations support the well know principle of toxicology that toxic agents often exhibit marked species differences in relative response to a hazardous agent. This supports the standard practice of generating experimental data from multiple species of animal models to assist with establishing levels which are protective of human health, particularly since humans also exhibit marked inter-individual differences in susceptibility to toxic agents. These early toxicological studies support the well-established practice of assessing the toxicological activity of a chemical of interest in multiple animal models to provide a scientifically sound basis for establishing precautions and regulations that protect the entire human population, including the most sensitive individuals.

Together, the studies by Von Wedel et al. (1943) and Miller (1944) indicate that PCBs are relatively easily absorbed through the skin and produce systemic toxicity though this route of exposure. Thus humans may be exposed to PCBs through inhaling PCB-contaminated air, ingesting PCB-contaminated food and water, and touching PCB-containing or PCB-contaminated materials.

In 1949, Laurence Fairhall authored a reference book for industrial hygienists and others in the chemical industry, government and academics entitled, Industrial Toxicology, (Williams and Wilkins Co., Baltimore). This reference book had a section on chlorinated diphenyl and chloronaphthalenes which states that systemic poisoning from these substances usually follows the inhalation of fumes and can result in acne and toxic jaundice produced by liver necrosis and occasionally lethality. He also states, "While acne may be taken as a warning sign in workers handling this material it is not invariably present and systemic poisoning may occur in the absence of this sign." Recommendations include medical supervision of workers with special care regarding the hygienic conditions of employment and with adequate ventilation. In 1949, the American Conference of Governmental Industrial Hygienists set a maximum allowable concentration value for chlorinated diphenyl of one mg/ cubic meter. It should be noted that this maximal allowable concentration exceeds the permissible limit for chlorinated diphenyl (with a 50-55% chlorine content) in the workplace of 0.5 mg/cubic meter proposed by Drinker, 1939.

Thus, during the 1930s and 1940s, academic researchers, the U.S. Public Health Service, Monsanto, and several large industrial users of PCBs became informed regarding the hazard that PCBs pose to the human health from inhalation, dermal and oral exposures to PCBs. Studies conducted during the 1930s and 1940s in laboratory animals confirmed the human observations that PCBs produce systemic toxicity, including liver injury, and at higher exposures, lethality.

During the 1930s and 1940s, the potential risk of human harm associated with PCBs was known in industry, academia, government and various other communities and organizations.

B. Studies in the 1950s Further Demonstrate the Toxic Effects of PCBs.

PCBs were known to cause adverse health effects in the 1950s, even at low levels of exposure. At no point did experimental studies report a safe level of PCB exposure. In 1955, The American Conference of Government Industrial Hygienists (ACGIH) set a threshold limit value (TLV) in air of 1 mg/m^3 for occupational exposure to vapors of PCBs (American Conferences of Government Industrial Hygienists Threshold Limits for 1955. AMA Arch. Ind. Health, 11:521, 1955). Based on an 8 hour exposure this would result in the inhalation of approximately 5mg of PCBs per day. This standard remained unchanged from that set in 1949 by the ACGIH.

This 1955 air standard for occupational exposure to PCBs was not protective of human health based on rat studies conducted during the 1930s and 1940s. Specifically, the TLV in air of 1 mg/m^3 for occupational exposure to vapors of PCBs exceeds the permissible limit in the work place of 0.5 mg/ cubic meter proposed by Drinker (1939) for chlorinated diphenyl (50 – 55% chlorine content).

Additional studies in the 1950s failed to identify a level of exposure that did not elicit an adverse effect and made clear the insufficiency of the ACGIH 1 mg/m^3 standard. In 1954, Yale University professors published an article on chloracne as observed in workers at a plant that contained PCB vapors from a leak in a heat exchange system which used chlorinated diphenyls. Meigs et al., (1954) reported that 5 to 19 months of intermittent exposure to an air concentration of 0.1 mg PCB/cubic meter was associated with seven cases of chloracne among 14 workers. This occupational health study clearly indicated that the occupational exposure limits were not adequate to protect human health, since multiple cases of chloracne were reported by Meigs et al. (1954) at PCB air levels that were 1/10th of the 1 mg/m^3 air standard, and 1/5th of Drinker's 0.5 mg/m^3 air standard.

In the mid-1950s, Monsanto Chemical Company funded a study to investigate the toxicity of the vapors of Aroclor 1242 and Aroclor 1254 (Treon et al., 1956). In one experiment, guinea pigs, rabbits, and rats were exposed for 7 hours on each of 82 days over a period of 120 days to air bearing the vapor of Aroclor 1242 at the concentration of 6.83 mg/m^3 (0.41 ppm). In another experiment, animals were exposed for 7 hours on each of 83 days over a period of 121 days to air containing Aroclor 1254 at the concentration of 5.4 mg/ m^3 (0.41 ppm). Inhalation exposure to PCBs under these conditions produced the following adverse effects: 1) A decrease in the rate of body weight gain in guinea pigs and rats exposed to Aroclor 1254. 2) A significant increase in the liver weight of rats exposed to Aroclor 1242 and Aroclor 1254. 3) A significant increase in the number of erythrocytes in rabbits exposed to Aroclor 1254. 4) A significant decrease in the number of leucocytes in guinea pigs exposed to Aroclor 1242. 5) A significant increase in hemoglobin in guinea pigs exposed to Aroclor 1242 and 1254.

In another set of experiments by Treon et al., (1956), animals were exposed to air containing Aroclor 1242 at a concentration of 1.9 mg/m^3 (0.18ppm) for 7 hrs/day for 150 days over a period of 214 days. Another group of animals was exposed to Aroclor 1254 at a concentration of 1.5 mg/m^3 (0.11ppm) for 7 hrs/day for 150 days over a period of 213 days. This

inhalation exposure to PCBs, at concentrations slightly higher than the 1 mg/m^3 recommended by the American Conference of Government Industrial Hygienists, resulted in liver damage. All of the rats exposed to Aroclor 1254 were found to have slight to moderately severe degenerative lesions of the liver. Rabbits exhibited diffuse hepatic degeneration which varied from cloudy to hyaline or hydropic degeneration and included varying degrees of fatty metamorphosis. Mice exposed to Aroclor 1254 had slight degenerative changes of the liver and exposed guinea pigs had slight alterations of hepatic cells characterized by cytoplasmic vacuolation. In addition, two of ten rats had chronic pyelonephritis, and the remainder had slight degeneration of the renal tubules. This study demonstrated that chronic, low level exposure to PCBs produced histopathological evidence of liver damage in four different species of laboratory animals and kidney damage in the rat. This adverse response was observed at air concentrations of PCBs slightly higher than the 1 mg/m^3 threshold limit value for occupational exposure recommended by the American Conference of Governmental Industrial Hygienists in 1955.

The experimental animal studies of Treon et al., (1956), clearly identifies the liver as a target organ for PCB toxicity, but most importantly, the study does not identify a level of exposure that does not elicit an adverse effect. Similarly, the occupational study by Meigs et al. (1954) reported that 5 to 19 months of intermittent exposure to an air concentration of 0.1 mg PCB/cubic meter produced chloracne in 7 out of 14 workers, but did not identify an exposure level that was not toxic. Furthermore, the studies during this time period did not analyze the effects of long-term exposures to very low levels of PCBs. To address the need to establish safe levels of exposure to hazardous agents, the Quarterly Bulletin of the Association of Food and Drug Officials of the United States (1954) suggested a 100-fold margin of safely as a reasonable safeguard to minimize the danger posed by toxic chemicals. The concept of including a 100-fold margin of safety was introduced at this time in an attempt to use toxicological results in animal studies to assist in establishing exposure levels that protect workers from the toxic effects of occupational exposures to PCBs.

C. Scientific Articles Published from 1958 to 1972 Continued to Document the Environmental and Health Hazards of PCBs.

During this period it became clear that PCBs were widely dispersed and persisted in the environment. PCBs were also found to bioaccumulate in food chains with the subsequent possibility of producing adverse effects on animals at the top of the food webs, including man. Considerable literature on the environmental hazards and toxicity of PCBs was published over this period of time. For example, a 114 page review article on the Environmental Impact of PCBs published in 1972 (Nelson, et al., Environmental Research 5: 249-362) contained 233 references to literature on PCBs. This review article contained information on the properties, production and uses of PCBs, transport and transformation of PCBs in the environment, environmental occurrence and human exposure to PCBs, toxic impurities in PCB formulations and toxicology of PCBs. As another example of the heightened interest and concern regarding PCBs, the entire first issue of Environmental Health Perspectives (185 pages, April, 1972) was devoted to PCBs. This issue contains the report of the Conference on PCBs, sponsored by the National Institute of Environmental Health Sciences (NIEHS) at the request of an Interdepartmental Task Force on PCBs. The conference was held at the Quail Roost Conference Center in Rougemont, N.C., on December 20-21, 1971.

Although PCBs were widely present in specimens analyzed for chlorinated hydrocarbon pesticides (for example DDT) in the 1950s and 1960s, they were generally understood as "unknown interfering compounds" until they were identified to be PCBs by Jensen (1966) and Widmark (1967). PCB residues were reported in fat samples of various wildlife species, particularly fish and fish-eating birds (Koeman et al., 1967; Lee et al., 1967; Holmes et al, 1967; Koeman et al., 1969) as well as human fat tissues (Lee et al., 1967; Biros et al., 1970) and human milk (Acker and Schulte, 1970). Aquatic animals and fish accumulate PCBs to levels of the order of 10,000 to 10,000,000 times higher than those in ambient water (ATSDR 2000). Due to their physical and chemical properties, PCBs have very low solubility in water, while the lipophilicity and chemical stability of PCBs results in their accumulation and biomagnification within aquatic food chains involving fish, birds and mammals. Top predators (birds, seals, rainbow trout, etc.) accumulate PCBs to levels as high as 10,000,000 times those found in ambient water (ATSRD 2000; EPA 1985; EPA 1989; EPA 2018). PCBs were consistently found in human fat, milk and blood plasma. Thus, breast feeding became recognized as a major route for exposure of infants to PCBs. Within a few years of their initial discovery as environmental pollutants, PCBs had become a well-known global contaminant (Gustafson, 1970). The environmental persistence of PCBs in conjunction with their ability to bioaccumulate in food chains and ultimately expose man contributed to the heightened concern regarding the environmental and health hazard of PCBs.

1. Early Indication of the Adverse Effects of PCBs on Animals in the Wild

Several cases have been reported in which PCBs may have caused damage to populations of wild animals. In a number of species of wild birds, primarily fish-eating or bird-eating predators, high PCB levels have been found in populations experiencing eggshell thinning, reproductive failure, population declines, and/or congenital abnormalities (Anderson et al., 1969; Vermeer and Reynolds, 1970; Risebrough et al., 1968, 1970; Risebrough and de Lappe, 1972; Postupalsky, 1971; Faber et al., 1972; Hays and Risebrough, 1972). The distribution of PCBs in the environment and the biota is highly correlated with that of other pollutants such as DDT and its metabolites and mercury. Thus, several environmental pollutants were implicated in producing adverse responses in populations of wild animals. In the case of PCBs, it can be stated with confidence that PCB levels in many ecosystems are higher than those which have been shown to cause adverse effects on reproduction and survival of representative species in the laboratory. It is therefore likely that PCBs are having adverse effects on populations of wild animals (Nelson et al., 1972).

Early studies found mink to be one of the most sensitive mammalian species. Nelson et al. (1972) reported the results of a feeding trial conducted by Aulerich. The study consisting of fifteen animals found that 30 ppm in the diet of equal parts of Aroclors 1242, 1248, and 1254 was fatal to all animals in 2 – 4 months.

Early studies in newly hatched chicks demonstrated that exposures to PCBs during the period of organogenesis (organ development) resulted in toxicity effecting several organ systems. Hydropericardium, occasionally accompanied by abdominal edema, kidney and liver damage were found in chickens fed Aroclor 1242 in the diet (McCune et al., 1962; Flick et al., 1965). Another study with 10-day old chickens reported mortality values after 25 day feeding of 16/30 at 50 ppm Aroclor 1248 in the diet, 4/20 at 40 ppm, 1/30 at 30 ppm and 0/10 at 10 ppm (Rehfeld et al., 1971).

Significantly, these early studies demonstrated that developing animals (embryonic and fetal period) are particularly sensitive to the toxicity of PCBs.

2. Early Indication that PCBs Produce Cancer in Laboratory Animals

In one of the earliest studies to investigate the carcinogenic activity of PCBs, Kimbrough et al., (1971, 1972) described morphological changes in livers of male and female Sherman strain rats fed 20, 100, 500, and 1000 ppm of Aroclors 1260 and 1254 in their diets for 8 months. Adenofibrosis was found in 1/10 males and 6/10 females fed 100ppm Aroclor 1254 and in 1/10 female rats fed 100 ppm Aroclor 1260. They also observed bladder cancers in two rats fed 100ppm of Aroclor 1260. Nagasaki et al., (1972) reported the hepatocarcinogenicity of Kaneclor-500, a Japanese PCB mixture, in male dd mice fed 500 ppm of PCBs. Together, these early studies provide experimental evidence supporting the carcinogenic activity of PCBs in two species of laboratory animals.

Allen and Norback (1973) reported induction of hyperplasia and dysplasia of gastric mucosa in male rhesus monkeys fed a diet containing 300 ppm of Aroclor 1248 for 3 months. Within one month, all of the PCB fed animals had hair loss from the head, neck, and back. A progressive, generalized, subcutaneous edema, particularly of the face, was manifested as swollen eyelids and lips. The concentration of PCBs within the experimental diet was less than an order of magnitude greater than that occurring in random food samples sold in the United States and less than levels that have occurred in food products as a result of industrial accidents. The increased cellularity, abnormal dysplastic growth pattern, and invasion of the adjacent tissue region indicate compromised gastric function and were believed by the authors to be suggestive of an eventual neoplastic transformation.

3. Early Indication of Immunosuppression in PCB Exposed Laboratory Animals

An immunosuppressive effect of PCBs was suggested by several observations. Vos and Koeman (1970) observed a reduction in lymphoid tissue in chicks. Vos and Beems (1971) reported lymphopenia in rabbits. Suppressed immune function was observed by Vos (1972), who reported that in guinea pigs, dietary exposure decreased antibody-forming cells after stimulation of the humoral lymphoid system with tetanus toxoid.

4. Early Indication of Developmental and Reproductive Effects in PCB-Exposed Laboratory Animals

Subsequent to early studies in chickens indicating that reproductive and developmental functions are particularly sensitive to PCBs during critical time periods (McCune et al., 1962; Flick et al., 1965). In another study, low mating indices and decreased survival of pups were reported for animals receiving Aroclor 1242 at 100 ppm and decreased survival of pups was observed for animals receiving Aroclor 1254 at 100ppm (Kelplinger et al., 1972).

Aroclor 1254 was also found to be toxic to pregnant rabbits and their offspring when treated for the first 28 days of gestation. Abortions, maternal deaths, and stillbirths were reported at oral doses as low as 12.5 mg/kg body weight/day (Villeneuve et al., 1971).

Keplinger et al., (1971) reported that chickens fed diets containing 10 or 100 ppm of Aroclor 1242 or 100 ppm 1254 exhibited loss of body weight, decreased thickness of egg shells, and poor hatchability of eggs. However, at exposure as high as 100 ppm Aroclor 1260 had no adverse effects. Keplinger et al., (1972) also reported that decreased hatchability was observed at dietary exposures at 6, 4, or 2 ppm.

In another study with chickens, decreased egg production and hatchability were noted at dietary exposure levels of 10 and 20 ppm Aroclor 1254 (Scott et al., 1971). Hatchability of eggs was reduced to about 72% of normal with a PCB level of 2.2 ppm in the eggs, and almost zero when the PCB level reached 4.5 ppm in the eggs. Peakall et al., (1972) reported that embryos from the second generation of Ring doves fed 10 ppm Aroclor 1254 exhibited a high frequency of chromosomal aberrations and a high incidence of embryonic death.

Together, rat, rabbit, chicken and dove studies support the profound sensitivity of developing avian and mammalian species to adverse reproductive and developmental effects of PCB exposures.

5. Severe Adverse Effects in Humans – Yusho and Yu-Cheng

In 1968, the accidental poisoning of over 1000 people in Japan with PCBs ("Yusho") was a dramatic example of the potential adverse health effects which can occur as a result of the production and wide-spread use of PCBs. In this case, an outbreak of poisoning that involved over 1000 people occurred in Northern and Western Japan where rice bran oil for human consumption was contaminated with Kanechlor-400, a PCB mixture containing 48% chlorine. The disease was named Yusho (rice-oil disease) (Kuratsune et al., 1969; Kuratsune et al., 1972). The contamination occurred because PCB mixtures used as heat exchangers in the manufacturing process leaked into the oil through pin holes in the pipes. This contaminated rice brand oil was then widely distributed for human consumption and resulted in unwanted PCB exposure and resulting injury in the population.

The latency period between ingestion of the oil and onset of clinical signs and symptoms was estimated at 5 – 6 months (Nelson et al., 1972). Minimal adverse effects have been estimated to occur at an exposure as low as 3 mg of PCBs per day over several months. However, the average doses associated with significant disease in the Yusho incident were in the range of 30 mg/day (Kolbye, 1972; Kuratsune et al., 1972). Adverse effects associated with Yusho include: chloracne, blindness, systemic gastrointestinal systems with jaundice, edema, abdominal pain, dark brown pigmentation of nails, distinctive hair follicles, increased sweating at palms, red plaques on limbs, itching, pigmentation of skin, swelling of limbs, stiffened sole and palm, feeling of weakness, numbness in limbs, fever, hearing difficulties, spasm of limbs, and headache (Kuratsune et al., 1969).

Newborn infants of poisoned mothers had skin discoloration, gingival hyperplasia with pigmentation and decreased birth weights due to the in utero exposure to PCBs. The skin of stillborn infants showed hyperkeratosis and atrophy of the epidermis and cystic dilation of hair follicles, along with the retention of PCBs in fetal tissues (Kojima et al., 1969). Thus, as early as 1969, there are dramatic findings of the profound toxicity of PCBs to the developing human

embryo and fetus, which are supported by experimental studies of adverse developmental and reproductive effects in PCB exposed rats, rabbits, chickens and doves.

In 1979, an accidental poisoning in Taiwan (Yu-Cheng) occurred due to the same cause as Yusho. Blood samples obtained from Yusho and Yu-Cheng patients who had been poisoned by ingesting contaminated cooking oils were analyzed for PCBs and polychlorinated dibenzofurans (PCDFs), a trace contaminant in the PCB contaminated cooking oil. At 11 years following the Yusho accident, the blood of patients contained PCBs but PCDFs were not detected, while 0.5 years after the Yu-Cheng accident, the patients with dermal lesions had blood containing PCBs and very low levels of PCDFs (about 500-fold less than the PCB level) (Kashimoto et al., 1985). Due to the high toxicity of PCDFs found in the Yu-Cheng patients' blood and in blood taken shortly after the Yusho accident, it is likely that PCDFs contributed in part to the toxicity observed in these patients.

6. Trace contaminants further contribute to the human health and environmental risk of PCBs.

PCBs are linked to two other toxic chemicals – PCDFs and PCDDs. PCDFs can be found at very low levels in PCB mixtures and may also be produced as a result of fires involving PCBs. PCDDs are not found in PCB mixtures, but may be created in fires involving PCBs.

PCDFs have been found at very low levels in commercial PCB mixtures (Vos et al., 1970; Roach and Pomerantz 1974; Bowes et al., 1975a,b; Nagayama et al., 1976). Aroclor 1242 was found to contain tetra-and pentachloridbenzofurans, with a total PCDF content of 4.5 ppm (Morita et al., 1978). Furthermore, the levels of PCDFs in PCB formulations increased with the length of time the PCBs were in service at high temperature as heat exchange media (Morita et al., 1978; Buser et al., 1978b) as originally suggested by Kuratsune et al. (1976). Polychlorinated dibenzofurans (PCDFs) are a group of halogenated tricyclic aromatic hydrocarbons, which consist of a total of 135 possible congeners. Like PCBs, they are persistent, wide-spread environmental contaminants which bioaccumulate in food chains and are found in human tissues. PCDFs are structurally and toxicologically similar to PCBs, however, PCDFs generally exhibit a greater toxic potency than PCBs. Thus the presence of low levels of PCDFs in some PCB formulations represents an additional environmental and health threat associated with the commercial use of PCB formulations.

Pyrolysis of PCB formulations at temperatures up to 700°C has been reported to produce PCDFs at concentrations up to 20,000ppm (Buser and Rappe, 1979; Buser et al., 1978a; Paasivirta et al., 1985). Accidental fires involving electrical transformers containing PCBs have been reported to produce PCDFs and PCDDs (Rappe et al., 1983, 1985; O'Keefe et al., 1985).

Polychlorinated dibenzodioxins (PCDDs) are a group of halogenated tricyclic aromatic hydrocarbons, which consist of a total of 75 possible congeners. Like PCBs and PCDFs, PCDDs are persistent, wide-spread environmental contaminants which bioaccumulate in food chains and are found in human tissues. PCDDs are structurally and toxicologically similar to PCBs and PCDFs. PCDDs and PCDFs have a similar toxic potency which is generally greater than that of PCBs. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD, dioxin) one of the 75 possible PCDDs, is the

most potent of the PCDDs and is the most toxic man-made chemical known. Thus, the formation of PCDDs during combustion of PCBs represents a significant environmental and health concern.

III. CURRENT KNOWLEDGE OF PCB TOXICITY

Observations and concerns relating to the toxicity of PCBs from 1930s-1970s have been confirmed by more recent studies which have documented that PCBs produce a broad range of adverse health effects.

A. Toxicity is Dependent on the Properties of Individual PCB Congeners.

Earlier studies focused on toxicological responses as a result of exposure to commercial PCB mixtures, such as Aroclor 1254 or 1248. As discussed previously in this report, PCB mixtures like Aroclor 1254 are made up of many different PCB congeners. These individual PCB congeners have different chemical and physical properties and exhibit specific toxicological responses. In addition, human and environmental specimens retain various individual PCB congeners which do not resemble that of Aroclor mixtures. Therefore, more recent studies have recognized these differences and focus on determining the potential toxicological effects of specific PCB congeners, rather than commercial PCB mixtures.

Generally, PCB congeners have been assigned to two general groups based on their chemical and spatial structure: dioxin-like PCBs (DL PCBs) and non-dioxin-like PCBs (NDL PCBs). DL-PCBs are aryl-hydrocarbon receptor (AhR) agonists and have biological and toxicological similarity to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD or dioxin), the most toxic man made substance known.

Twelve DL-PCB congeners (with no or only one chlorine on the ortho positions of the biphenyl molecule) exhibit dioxin-like activity and have been assigned Toxic Equivalency Factors (TEFs), which represent the toxic potency of dioxin-like PCBs relative to TCDD (TEF = 1.0). This is in addition to 17 PCDDs and PCDFs with chlorine at the 2, 3, 7, and 8 positions that are recognized as being dioxin-like compounds (DLCs) (Van den Berg et al., 2006). The dioxin-like PCBs contain from four to seven chlorines on the biphenyl molecule, with no more than one chlorine on the *ortho*-positions of the biphenyl molecule (2, 2’, 6, or 6’ positions). For example, the biphenyl rings of the dioxin-like PCBs, PCB 77 (3,3′,4,4′-tetrachlorobiphenyl) and PCB 126 (3,3′,4,4′,5-pentachlorobiphenyl), assume a coplanar orientation that mimics the planar structure of 2,3,7,8-TCDD and are capable of binding to the aryl hydrocarbon receptor (AhR), also known as the Dioxin Receptor. PCB 126 (3,3’,4,4’,5-pentachlorobiphenyl) is the most toxic of the dioxin-like PCBs with a TEF of 0.1, which is one tenth as potent as TCDD (Van den Berg et al., 2006). Chronic low-level exposure to dioxin-like compounds (DLCs), such as dioxin-like PCBs results in prolonged activation of AhR and subsequently the up- and down-regulation of genes which lead to an increased risk of cancer and a number of non-cancer health effects (Ovando et al., 2010; Vezina et al 2004; Van den Berg et al., 2006; NTP 2006b, Schecter 2012). Since dioxin-like PCBs act by the same AhR pathway as dioxin, Toxic Equivalents (TEQs) are used to express the toxic potency of complex mixtures of dioxin-like PCBs in terms of TEQs. PCB TEQs in a specimen are calculated as the sum of the concentration of each dioxin-like PCB times the respective TEF

for that PCB congener. TEQs for dioxin-like PCBs in human blood are generally expressed in terms of ppt (parts per trillion, pg/g serum lipid), with one ppt TEQ for DL PCBs being toxicologically equivalent to one ppt of TCDD or dioxin in the given specimen.

The remaining 197 PCB congeners are considered non-dioxin like PCBs (NDL-PCBs) which have very low or no activity towards the AhR, yet exhibit significant toxicological activity (Pessah et al. 2010). The NDL-PCBs are more abundant in the environment, wildlife and humans. Related mechanisms responsible for the toxicological activity of NDL PCBs include: (1) disruption of thyroid hormone metabolism and signaling (Knerr & Schrenk, 2006; Zoeller, 2005, 2007) and (2) perturbations in cellular Ca^{2+} signaling (Pessah et al. 2010). Many NDL-PCBs enhance the activity of ryanodine receptors (RyRs), which are a family of intracellular Ca^{2+} channels that mediate the release of calcium ions within cells, leading to adverse responses (Wong & Pessah, 1996; Pessah et al., 2006). Pessah et al (2006) has proposed a structure-activity relationship for NDL-PCB congeners toward the ryanodine receptor-Ca^{2+} channel complex type 1 (RyR1). Significant to the neurotoxic potential of NDL-PCBs, RyR channel activity regulates a variety of physiological and pathophysiological processes in the central and peripheral nervous systems (Pessah et al. 2010). Decrements in neonatal reflexes, cognitive function, motor activity, tremors, changes in autonomic functioning, and hearing impairments are consistent findings with developmental PCB exposures in studies of humans and animals, and are primarily attributed to adverse effects on the developing CNS (Darras, 2008; Fitzgerald et al., 2008; Kenet et al., 2007; Mariussen & Fonnum, 2006; Roegge & Schantz, 2006; Stewart et al., 2000, 2008; Schantz et al., 2003; Boucher et al., 2009, 2014; Berghuisa and Roze 2019). Additionally, PCB toxicity in excitable and non-excitable cells appears to be mediated at least in part by oxidative stress and involves biotransformation via quinone and hydroxylated metabolites, and altered activities of key anti-oxidant defense enzymes such as glutathione transferases, and NADH/NAD(P)H oxidoreductases (Duntas, 2008; Howard et al., 2003; Y. Liu et al., 2009; Murugesan et al., 2007; Wei et al.,2009).

B. <u>Background on Cancer and Mechanisms for the Carcinogenicity of PCBs</u>

It is generally accepted that carcinogenesis is a multistage process, consisting of initiation, promotion, and progression. Initiation occurs at the cellular level where one or more cells in the body exhibits a DNA modification or mutation that can be fixed upon cell division and passed on to daughter cells which retain the DNA mutation. Each day many cells in the body express DNA mutations. While genotoxic chemicals will increase the number of initiated cells in the body, many cells exhibit DNA mutations each day without exposure to genotoxic chemicals, simply due to the complex processes associated with DNA replication and the very large number of cell divisions which occur each day in the body. Promotion is a process that does not involve producing a DNA mutation, but which stimulates the division and clonal expansion of the initiated cell population. Along with increasing the rate of cell division of initiated cells, promotion can include a reduction in apoptosis or programmed cell death in the population of initiated cells. This leads to altered regulation of cell division and differentiation. Progression is the process which follows initiation and promotion, leading to further DNA damage and visible chromosome disarrangements within cells. This irreversible damage results in a malignant neoplastic state, commonly known as cancer. The process of initiation followed by promotion is necessary for an initiated or mutated cell to develop into cancer.

Mechanistically, both non-dioxin-like and dioxin-like PCBs act as tumor promoters. Van der Plas et al., 2000 reported that about 80% of the tumor promoting activity of PCBs was found in the NDL PCBs, with from 2 to 4 ortho-substituted chlorines on the biphenyl molecule, which have little or no dioxin-like activity. In addition, there is growing evidence that PCBs have genotoxic or tumor initiating activity. Initiation involves a change in the DNA sequence or quantity, i.e. either a gene mutation, chromosome mutation (breaks, rearrangements), or genome mutation (change in the number of chromosomes). Sandal et al. (2008) compared the genotoxic activities of PCB 52 (2,2′,5,5′ tetrachloro biphenyl, a non-dioxin-like congener) and PCB 77 (3,3′,4,4′ tetrachlorobiphenyl, a dioxin-like congener) on cultured human lymphocytes. They found that both congeners caused DNA damage as monitored by the comet assay, but that PCB 52 is significantly more potent. Both PCB 9 (2,5 dichlorobiphenyl) (Yilmaz et al., 2010) and PCB 11 (Zhu et al., 2013) generate reactive oxygen species, known to be a risk factor for cell damage and death. Ludewig et al. (2008) found that PCB 3 (4-monochlorobiphenyl) and/ or its metabolites increase mutations in rat liver. Ludewig and Roberston (2013) reviewed the literature and concluded that lower chlorinated biphenyls may be readily bioactivated to reactive intermediates, arene oxides and particularly quinones, with the generation of reactive oxygen species (ROS). These reactive species can interact with DNA and with protein forming covalently bound adducts which are most likely the cause for the observed gene, chromosome, and genome mutations.

Liu et al. (2017) demonstrates that PCB 22 (2,3,4'-tri-CB), PCB 20 (2,3,3'-tri-CB), PCB 74 (2,4,4',5-tetra-CB) and PCB 52 (2,2',5,5'-tetra-CB) induced micronuclei and/or gene mutations in mammalian cells and that among several human CYP enzymes, human CYP2E1 is most efficient in activating these PCBs to mutagenic metabolites. The induction of gene mutations in human CYP2E1-expressing Chinese hamster V79 cells by PCB 22 and 74 was more potent than that of *N*-nitrosodimethylamine, a potent known carcinogen activated by human CYP2E1.

Thus, the experimental results provide evidence that the carcinogenic activity of PCBs is a result of their ability to act as genotoxic (mutagenic) tumor initiators and tumor promoters.

C. <u>Cancer and Non-Cancer effects of Aroclor PCB Mixtures in Laboratory Animal Studies</u>

1. Non-Cancer Effects in Laboratory Animals

The U.S. EPA's Integrated Risk Information System (IRIS) Program supports the mission of EPA by identifying and characterizing the cancer and non-cancer health hazards of chemicals found in the environment. Following a comprehensive review of toxicity data, the U.S. EPA issued an IRIS report in 1994 for the non-cancer risks associate with exposure to Aroclor 1248 (U.S. EPA, IRIS 1994). The IRIS review group identifies critical, sensitive adverse responses and attempts to establish a reference dose (RfD), which is defined as an exposure to a chemical agent in the human population that is likely to be without an appreciable risk of deleterious effects during a lifetime. Derivation of an oral RfD for Aroclor 1248 was not recommended because a frank effect (death of an infant) was noted at the lowest dose tested in a sensitive animal species, the rhesus monkeys (Macaca mulatta). Schantz et al. (1989) evaluated neurobehavioral performance in offspring of rhesus monkeys that had been exposed to 0.03, 0.1 and 0.2 mg/kg-day of dietary Aroclor 1248 for different durations. A dose-dependent increase in developmental toxicity was observed in the offspring, which included the lowest dose (0.03 mg/kg-day), where one of seven

infants died at the time of weaning and showed signs of PCB intoxication that included thymic atrophy and skin hyperpigmentation. Other earlier studies also support the sensitivity of the monkey to the reproductive, developmental and immunotoxic effects of PCBs (Barsotti et al., 1976; Thomas et al., 1978), suggesting that humans will have similar serious health risks associated with low exposure to PCBs.

In 1993, the U.S. EPA IRIS work group issued an RfD for Aroclor 1016 of 0.00007 mg/kg-day (0.07 µg/kg-day) based on reproductive and developmental studies conducted in rhesus monkeys (U.S. EPA, IRIS 1993). Aroclor 1016 is a commercial mixture (average chlorine content of 42%) which was prepared by the fractional distillation of Aroclor 1242, which excluded the higher boiling (i.e., more highly chlorinated) congeners and was devoid of chlorinated dibenzofurans, including those with dioxin-like activity. Total TEQ contributions (ppm) in Aroclor 1016, 1242, 1254, and 1260 are 0.11, 7.8, 23.4 - 47.6, and 7.2, respectively (Mayes et al., 1998). This is of importance since the adverse health effects of Aroclor 1016 can be attributed to non-dioxin like PCBs. Effects occurring in the offspring of monkeys that ingested 0.007 or 0.028 mg/kg-day doses of Aroclor 1016 for approximately 22 months consisted of hairline hyperpigmentation at greater than or equal to 0.007 mg/kg-day, and decreased birth weight and neurologic impairment at 0.028 mg/kg-day (Barsotti et al., 1984; Levin et al., 1988; Schantz et al., 1989, 1991). Based on the reduced birth weights of prenatally-exposed monkeys, the 0.007 mg/kg-day dose is the no observable adverse effect level (NOAEL) and the 0.028 mg/kg-day dose is a lowest observable adverse effect level (LOAEL) in monkeys. Deficits in birth weight and head circumference and behavioral dysfunctions, including deficits in visual recognition, short-term memory, and cognitive function also have been observed in infants of human mothers who consumed fish contaminated with PCB mixtures of unknown composition (Fein et al., 1984; Jacobson et al., 1985, 1990a, 1990b, 1992; Jacobson and Jacobson 1996; Boucher et al., 2009).

In 1994, the U.S. EPA IRIS work group issued an RfD for Aroclor 1254 of 0.00002 mg/kg-day (0.02 µg/kg-day) based on clinical and immunological abnormalities in Rhesus (Macaca mulatta) monkeys ingesting Aroclor 1254 daily at dosages of 0.005-0.08 mg/kg-day for more than 5 years. The animals showed an increase in ocular exudate, prominence and inflammation of the Meibomian glands and distortion in nail bed formation. These changes were seen at the lowest dose tested, 0.005 mg/kg-day, and had a dose-dependent response (Arnold et al. 1993a, 1993b). Impaired immunological functions at this low exposure include decreases in IgM and IgG antibodies in response to sheep red blood cells (SRBC) which involves participation by the three principal cells of the immune system: the macrophage, B lymphocytes and T lymphocytes (Tryphonas et al., 1989, 1991a, 1991b; Luster et al., 1994). Support for the LOAEL is provided by the occurrence of minimal immunological alterations in monkeys at 0.0075 mg/kg/day, as well as clinical signs of toxicity (ocular and dermal changes) and decreased antibody responses in offspring of monkeys that were exposed to a similar dose level of Aroclor 1254 (0.005 mg/kg/day) for approximately 46 weeks during gestation and nursing.

2. Cancer Effects in Laboratory Animals

The U.S. EPA's Integrated Risk Information System (IRIS) Program supports the mission of EPA by identifying and characterizing the cancer and non-cancer health hazards of chemicals found in the environment. In 1994, the U.S. EPA IRIS work group conducted a quantitative risk assessment for the carcinogenic activity of PCBs from oral and from inhalation exposures (U.S.

EPA 1996a, 1996b, IRIS 1994). At that time, the human carcinogenicity data was not conclusive but the animal data clearly supported the carcinogenic activity of PCBs. Statistically significant, dose-related, increased incidences of liver tumors (liver adenomas or carcinomas, hepatocholangiomas) were induced in female rats by Aroclors 1260, 1254, 1242, and 1016 (Brunner et al., 1996; Mayes et al., 1998). Thyroid gland follicular cell adenomas or carcinomas were increased in males for all Aroclors, while only Aroclor 1260 produced liver tumors in male rats (Brunner et al., 1996). These results are consistent with earlier rat studies of Aroclor 1260 (Kimbrough et al., 1975; Norback and Weltman 1985). The National Cancer Institute also conducted a cancer bioassay in rats receiving Aroclor 1254 in the diet and reported an increased incidence of hepatocellular adenomas and carcinomas (NCI, 1978). A significant increase in gastric adenocarcinomas was also reported in the NCI Aroclor 1254 study, and the intestinal metaplasia suggests that Aroclor 1254 can act as a tumor initiator (Morgan et al., 1981 and Ward 1985). The comprehensive cancer studies with the commonly used commercial PCB mixtures, including Aroclors 1260, 1254, 1242, and 1016, were designed to reflect exposures to the complex range of PCB congeners most frequently found in environmental mixtures, and various organisms, including humans. Total TEQ contributions (ppm) in Aroclor 1016, 1242, 1254, and 1260 are 0.11, 7.8, 23.4 - 47.6, and 7.2, respectively (Mayes et al., 1998). <u>This is of importance since the carcinogenic activity of Aroclor 1016 can be attributed to non-dioxin like PCBs.</u> The rat studies with Aroclor 1016 also support the IARC 2016 conclusion that that the carcinogenicity of PCBs cannot be solely attributed to the carcinogenicity of the dioxin-like PCBs

Based on the analysis of the dose-dependent cancer responses reported by Brunner et al. (1996) and Norback and Weltman (1985), the U.S. EPA estimated that drinking water containing 0.1 µg PCBs/liter of water is associated with one excess cancer in 1,000,000 persons. Similarly, the cancer risk was estimated at 10 excess cancer case in 1,000,000 persons with drinking water containing 1.0 µg PCBs/liter. The U.S. EPA also estimated that ambient air containing 10 ng PCBs / cubic meter is associated with one excess cancer in 1,000,000 persons. This is of major concern since PCB air concentrations in indoor air in many school building are in excess of 100 ng PCBs/cubic meter, which is estimated to result in 10 excess life time cancer cases in 1,000,000 persons (U.S. EPA IRIS 1996a; U.S. EPA 2012).

3. Cancer and Non-Cancer Effects of different PCB congeners in 2-Year Rat Studies Conducted by the National Toxicology Program (NTP)

More recently, the National Toxicology Program (NTP) conducted chronic studies in rats to assess the cancer and non-cancer effects of expose to individual dioxin-like and non-dioxin-like PCBs. In addition, they assessed the toxicity of a binary mixture of a dioxin-like and a non-dioxin-like PCB, which was found to have an enhanced or more than additive toxicity.

The NTP conducted multiple 2-year lifetime rat bioassays to evaluate the chronic toxicity and carcinogenicity of dioxin-like compounds (DLCs) and structurally related PCBs individually and in defined mixtures. As expected, PCB 126 (3,3'4,4'5pentachlorobiphenyl), the most potent dioxin-like PCB, exhibited responses similar to that observed for 2,3,7,8-TCDD, including cholangiocarcinoma and hepatocellular adenoma of the liver, cystic keratinizing epithelioma (CKE) of the lung, and gingival squamous cell carcinoma (SCC) of the oral mucosa (Walker et al., 2005; NTP 2006b). In contrast to PCB 126, exposure to PCB 153, a non-DLC, did not produce

these responses but still yielded increased incidences of nonneoplastic lesions of the liver, thyroid gland, ovary, oviduct, and uterus in female rats (NTP 2006a).

Results from another NTP study demonstrated a marked potentiation of the hepatotoxicity and carcinogenicity of PCB 126 in female SD rats that received a combined chronic exposure to PCB 126 and PCB 153 (2,2',4,4',5,5'hexachlorobiphenyl) (NTP 2006c). PCB 126 is the most potent dioxin-like PCB, with a TEF of 0.1 (1/10th that of 2,3,7,8-TCDD). PCB 153 (TEF = 0) is one of the most abundant non-dioxin like PCBs (NDL PCB) in humans and the environment. The NTP chronic cancer bioassay of PCB 126 alone supported the use of TEFs for the carcinogenic activity of PCB 126 (Walker et al., 2005). While exposure to PCB 153 alone produced mild hepatotoxicity, with the exception of hepatic hypertrophy, and no cancer, co-administration of increasing doses of PCB-126 with a constant concentration of PCB-153 in rats lead to increasing incidences of hepatocellular adenoma and cholangiocarcinoma, suggesting a more-than-additive effect (NTP 2006c). The results strongly support the conclusion that PCB 153 is potentiating the hepatotoxicity and carcinogenicity of the dioxin-like PCB 126. This is important since humans are exposed to mixtures of dioxin-like PCBs (for example 126) and non-dioxin like PCBs (for example 153).

The NTP also conducted a 2 year study, assessing the cancer and non-cancer effects of chronic exposure to 2,3', 4,4'5-pentachlorobiphenyl (PCB 118), which has very low dioxin-like activity (TEF= 0.00003) (NTP 2010). The study found clear evidence of carcinogenic activity of PCB 118 in female Harlan Sprague-Dawley rats based on increased incidences of neoplasms of the liver (cholangiocarcinoma, hepatocholangioma, hepatocellular adenoma), lung (cystic keratinizing epithelioma) and uterus. Administration of PCB 118 caused increased incidences of non-cancer lesions including hypertrophy, hyperplasia, fibrosis, and toxic hepatopathy of the liver, metaplasia of the lung, atrophy of the adrenal cortex, inflammation and cytoplasmic vacuolization of the pancreas, and hypertrophy of the thyroid gland. Exposure to PCB 118 also lead to dose-dependent decreases in the concentrations of serum total thyroxine (T_4) and free T_4 in all dosed groups.

Together, the extensive results obtained from the NTP rat studies of low-level, long-term exposure to selected PCB congeners indicates that the carcinogenic and non-carcinogenic responses are due to both the dioxin-like (DL) and non-dioxin like (NDL) activities of PCB congeners. The observation that NDL-PCB 153 potentiated the hepatotoxicity and carcinogenicity of the dioxin-like PCB 126 indicates that combined, real world exposures to various PCB congeners may lead to more than additive risk of adverse outcomes, and the need to reduce human exposures to all PCB congeners to protect human health.

D. Adverse Health Effects in Humans Exposed to PCBs

Adverse health effects that have been associated with exposure to PCBs in humans include, but are not limited to, cancer, developmental effects, diabetes, liver injury, immune system dysfunction, neurobehavioral effects, impaired thyroid function, reproductive system impairment, cardiovascular disease and chloracne (ATSDR 2000; ATSDR 2011; EPA 1985; EPA 1989; EPA 2018; IARC 2016).

1. Developmental and Neurodevelopmental Effects in Humans Exposed to PCBs

PCB exposures of vulnerable populations, including pregnant women, fetuses, infants, and children are of heightened concern because these sensitive populations are undergoing growth and differentiation, particularly during critical periods for brain development.

Toxic effects of PCBs in humans were first indicated by acute high exposure in adulthood, either from high occupational exposure or contaminated food, resulting in skin rashes, weakness, and liver disease (Hsu et al., 1985; Kuratsume et al., 1972; Fischbein et al., 1979). Further studies have also demonstrated the importance of developmental exposure, as the offspring of the acutely exposed adults show signs of reduced fetal and childhood growth and neurodevelopmental issues (Guo et al., 1995; Yamashita and Hayashi, 1985; Chen et al., 1994). Chronic exposure during development via maternal consumption of PCB contaminated Great Lake fish or with environmental exposures has been tied to reduced fetal growth, impaired cognitive function and neurodevelopmental problems in infants and young children (Fein et al., 1984; Jacobson et al., 1985, 1990a, 1990b, 1992; Jacobson and Jacobson 1996; Darvill et al., 2000; Stewart et al., 2003; Rogan and Gladen, 1991). Similar effects have been found in more recent studies that measured specific congeners in maternal blood or placental tissue in humans, including shorter gestational length with mono-chlorinated NDL PCB congeners (Kezios et al., 2012), reduced IQ with heavily chlorinated NDL congener (Stewart et al., 2008) reduced motor development with DL and NDL congeners (Berghuis et al., 2013).

a. Fetal Growth

Recent studies have added to the mounting evidence that low-level exposures to PCBs are associated with reduced fetal growth. Govarts et al 2012, conducted a meta-analysis within 12 European birth cohorts, comparing birth weight, adjusted for gestational age, and cord blood PCB 153. The analysis found a birth weight decline of 150 g [95% confidence interval (CI): –250, –50 g] per 1-μg/L increase in PCB-153, but found no effect for *p,p´*-DDE levels. Following this study, Verner et al 2013, suggested that this association between PCB levels and birth weight may be attributable to the confounding factor of maternal weight gain during pregnancy. Pharmacokinetic analysis found that gestational weight gain, which is associated negatively with PCB levels in maternal and cord blood, and positively with birth weight, could confound this association.

A prospective study design can address pharmacokinetic concerns associated with gestational weight gain (Verner et al. 2013). In a prospective pregnancy study with preconception enrollment of couples, Robledo et al. 2015, extended the work Murphy et al 2010, and demonstrated that both preconception maternal and paternal serum concentrations of persistent organic pollutants were significantly associated with birth size measures among their offspring. Birth weight among boys was lower by 99–170 g per 1-SD increase in ln-transformed maternal (PCBs 138, 153, 167, 170, 195, and 209) and paternal (PCBs 172, 195) concentrations. Both maternal and paternal serum concentrations PCBs 128, 138, 167, and 195 were associated with deduced birth weight, head circumference, length, or ponderal index (weight/height^3). Together, the results support the conclusion that preconceptional maternal and paternal concentrations of several PCBs, during the critical preconception window, were associated with statistically significant reductions in birth size among offspring.

Casas et al. (2015) conducted a larger study using a pooled dataset of 9377 mother–child pairs enrolled in 14 study populations from 11 European birth cohorts to explore exposure–response relationship between PCB-153 and p,p′-DDE and birth outcomes. Casas et al. (2015) observed an inverse linear exposure–response relationship between prenatal exposure to PCB-153 and birth weight [decline of 194 g (95% CI −314, −74) per 1 μg/L increase cord serum PCB-153] in regression analysis adjusted for cohort, maternal age at delivery, parity, child's sex, maternal pre-pregnancy BMI, maternal height, maternal smoking during pregnancy, maternal education, time of sample collection, gestational age, and the square of gestational age. A reduction in birth weight was observed over the entire exposure range, including those at low levels. This reduction was stronger among children of mothers who were non-Caucasian or had smoked during pregnancy. The most susceptible subgroup was girls whose mothers smoked during pregnancy. After adjusting for absolute gestational weight gain or estimated fat mass, a reduction in birth weight was still observed. This study suggests that the association between low level exposure to PCB-153 and birth weight exists and follows an inverse linear exposure–response relationship with effects even at low levels, and that maternal smoking and ethnicity modify this association.

Using data from the Avon Longitudinal Study of Parents and Children, Patel et al. (2018) investigated the association between prenatal exposure to PCBs (blood collected during pregnancy) and fetal growth in a sample of 448 mother-daughter pairs. Daughter's birth weight was −138.4 g lower (95% CI: −218.0, −58.9) for each 10 ng/g lipid increase in maternal serum PCB-118, −41.9 g lower (95% CI: −71.6, −12.2) for every 10 ng/g lipid increase in maternal serum PCB-153, and −170.4 g lower (95% CI: −306.1, −34.7) for every 10 ng/g lipid increase in maternal serum PCB-187, among girls with mothers in the lowest education group which is a possible marker for socioeconomic status.

The Tohoku Study of Child Development, examining 489 mother-newborn pairs, found that total PCBs in cord blood was significantly associated with reduced birth weight in both male and female newborns, even after adjusting for possible confounders (Tatsuta et al., 2017). However, a negative association of total mercury with birth weight was found only in the male newborns and there was no significant relationship between lead and birth weight in both groups. Thus, these findings support those of other studies which found that general, environmental background levels of maternal PCBs are associated with reduce birth weight.

Similarly, the Norwegian Mother and Child Cohort Study also showed the association of PCB levels with low birth weight and deduced head circumference (Papadopoulou et al. 2013). In a study in Chiba, Japan, Eguchi et al. (2019) found that PCB concentrations in maternal serum were weakly and negatively related to birth weight, whereas trace elements (mercury, manganese, selenium, and cadmium) were not associated with birth weight. Serum PCB and manganese levels were negatively associated with head circumference, whereas other trace elements were not associated with head circumference when adjusted for exposure levels of other contaminants, and maternal and fetal characteristics.

Tang et al. (2018) conducted a cross-sectional study to analyze the associations between PCB levels in umbilical cord serum and reproductive hormones and birth outcomes of mothers and newborns. Follicle-stimulating hormone (FSH) was decreased by all PCB congeners and reached statistical significance with PCB 101. Luteinizing hormone (LH) was decreased by all

PCBs (except 180) and reached statistical significance with PCB 52. Testosterone (T) was decreased by all PCBs (except 138) and reached statistical significance with PCB 28 in all newborns and PCB 118 in males only. Head circumference was decreased by all PCBs (except 138) and reached statistical significance for PCBs 101 and 118. Gestational age was reduced by most PCBs and reached statistical significance with PCBs 28 and 101. Thus, PCBs in umbilical cord blood are negatively associated with reproductive hormone levels and negatively affect birth outcomes.

Iszatt et al. (2015) investigated the impact of prenatal and postnatal exposure to PCB 153 and p,p´-DDE on infant growth. Pooled data from seven European birth cohorts with biomarker concentrations of PCB-153 (n = 2,487), and p,p´-DDE (n = 1,864) was used to estimate individual specific cord blood concentration (prenatal exposure) and cumulative postnatal exposure using a validated pharmacokinetic model (Verner et al. 2013). The validated pharmacokinetic model generated exposure profiles based on cord blood, maternal blood, or breast milk levels and known determinants of children's blood concentration. Growth was assessed as the change in weight between birth and 24 months. A significant increase in growth was associated with p,p´-DDE, due to prenatal exposure (per interquartile increase in exposure, adjusted $\beta = 0.12$; 95% CI: 0.03, 0.22). In contrast, a significant decrease in growth was associated with postnatal PCB-153 exposure ($\beta = -0.10$; 95% CI: –0.19, –0.01). Grandjean et al. (2003) also reported attenuated growth of breastfed children exposed to major PCB congeners (138, 153, and 180) at 18 months. Iszatt et al. (2015) concluded that using state-of-the-art exposure modeling, postnatal PCB-153 was associated with decreased growth at European exposure levels of PCB-153, which is a marker of total PCB exposure.

With the exception of some earlier reports (Chao et al. 2003; Gladen et al. 2003; and Longnecker et al. 2005), reduced birth weight and/or head circumference are consistently reported as sensitive effects of PCBs on fetal development in most studies. The adverse effects of PCBs on fetal growth support the need to minimizing PCB exposures in infants, pregnant women and women of childbearing age.

b. Neurodevelopment

Several articles have reviewed published animal and human studies investigating the association of PCB exposures with developmental neurotoxic and neurobehavioral / neuropsychological deficits, cognitive development, attention deficit / hyperactivity disorder, and motor development (Polanska et al., 2013; Grandjean and Landrigan 2006; Majidi et al. 2013; Kodavanti, 2005; Pessah et al., 2010; Yang et al., 2009; Eubig et al., 2010; Boucher et al., 2009). Epidemiologic data indicate that PCBs negatively impact neuropsychologic function in exposed children (Carpenter 2006; Korrick and Sagiv 2008; Schantz et al. 2003; Boucher et al. 2009), and experimental animal studies confirm that developmental PCB exposure causes cognitive and psychomotor deficits (Mariussen and Fonnum 2006). PCBs interfere with endocrine functions, specifically those mediated by thyroid hormone (Zoeller 2007) and estrogen (DeCastro et al. 2006; Dickerson and Gore 2007), and increase neuronal Ca2+ levels via several mechanisms (Kodavanti 2005; Mariussen and Fonnum 2006), including ryanodine receptor (RyR) activation (Pessah and Wong 2001). Endocrine modulation in turn can influence neuronal connectivity via dynamic

control of dendritic structure. Winneke (2011) suggested a plausibility for PCB-related neurodevelopmental adversity due to PCB induced thyroid dysfunction and oxidative stress.

Boucher et al., (2009) critically reviewed published results from nine longitudinal prospective birth cohorts with biologic markers of prenatal PCB exposure and indicators of cognition from infancy to childhood. Following review of the published data, the authors state that, "The most consistent effects observed across studies are impaired executive functioning related to increased prenatal PCB exposure. Negative effects on processing speed, verbal abilities, and visual recognition memory were also reported by most studies. Converging results from different cohort studies in which exposure arises from different sources make it unlikely that co-exposure with another associated contaminant is responsible for the observed effects." The authors conclude that, "this review supports the existence of specific, detrimental effects of prenatal exposure to environmental levels of PCBs on neuropsychological functioning in children. Executive function impairments were mainly outlined. Failure to assess this specific aspect of cognition may explain why some studies did not find significant relationships between prenatal PCB exposure and cognitive development. These effects, along with possible slower information processing and impairments in verbal abilities and visual memory, can be responsible for the IQ effects observed in most studies."

Similar conclusions were also reported in the earlier review on effects of PCB exposure on neuropsychological function in children (Schantz et al., 2003). Studies in Michigan, Oswego, New York, Holland, Germany, and the Faroe Islands have all reported negative associations between prenatal PCB exposure and measures of cognitive functioning in infancy or childhood, while only one published study in North Carolina has failed to find an association between PCB exposure and cognitive outcomes. "It is particularly noteworthy that the levels of exposure in some of the more recent studies, the Oswego cohort, for example, are significantly lower than in the earlier studies, yet negative impacts on cognitive functioning are still being reported."

The relationship between prenatal PCB exposure (placenta PCB levels) and intelligence (IQ) was assessed in 9-year-old children from Oswego NY, a town on the south shore of Lake Ontario (Stewart et al., 2008). Since the placenta originates from both maternal and fetal tissue, it provides an appropriate tissue for PCB measurements, representing prenatal PCB exposure. For each 1-ng/g (wet weight) increase in PCBs in placental tissue, Full Scale IQ dropped by three points ($p = 0.02$), and Verbal IQ dropped by four points ($p = 0.003$). Moreover, this association was significant after controlling for many potential confounders, including prenatal exposure to methylmercury, dichlorodiphenyldichloroethylene (DDE), hexachlorobenzene, and lead. Stewart et al. (2012) published an updated assessment of the relationship between placenta PCB levels and average IQ data in children from Oswego, NY at 9 and 11 years of age. PCBs predicted lower IQ at both ages; and hexachlorobenzene (HCB) appeared as a significant predictor of IQ at the 11-year assessment, while neither DDE nor mirex was related to lower IQ at either age. However, analysis of the IQ data set as a whole showed that both PCBs and HCB predicted lower IQ in a generally independent fashion. In the analysis at 11 years of age, the Freedom from Distractibility Index (an intelligence index that measures a person's short term attention span and concentration span) remained significantly lower when controlling for HCB. The results indicate that prenatal PCB exposure in the Great Lakes region is associated with lower IQ in children, supporting similar

studies conducted 10 years earlier (Fein et al., 1984; Jacobson et al., 1985, 1990a, 1990b, 1992; Jacobson and Jacobson, 1996).

Effects of PCBs were detected in infancy on visual recognition memory in several studies (Jacobson et al., 1985; Darvill et al., 2000; Boucher et al., 2014). In most studies, prenatal exposure was associated with adverse effects on cognition in childhood, including poorer IQ scores and response inhibition (Jacobson and Jacobson, 1996, 2003; Stewart et al., 2005). Altered motor development has also been reported, especially gross motor function during infancy as assessed using the Psychomotor Development Index of the Baylay Scales of Infant Development (Koopman-Esseboom et al., 1996; Rogan and Gladen, 1991; Walkowiak et al., 2001). Lower psychomotor scores in infants were associated with transplacental (prenatal) PCB exposure in earlier studies by Rogan and Gladen 1991 and Koopman-Esseboom et al., 1996. Detrimental effects of postnatal PCB exposure from breastfeeding was also reported for mental and motor development in children between 7 and 42 months of age (Walkowiak et al., 2001), which were no longer evident when these children were re-assessed at 6 years of age (Winneke et al., 2005). While this may be suggestive of a PCB-related neurodevelopmental delay, it is not supported by the PCB related deficits in IQ in 11-year-old children of the Michigan cohort (Jacobson and Jacobson 1996) and with loss of IQ in 9-year-old children relative to prenatal PCB exposure in the Oswego (Lake Ontario) cohort (Stewart et al., 2008).

Walkowiak et al. (2001) conducted a study in Dusseldorf, Germany of 171 healthy mother-infant pairs and prospectively measured psychodevelopment in newborn infants aged 7, 18, 30, and 42 months to assess the impact of background environmental PCB levels on neurodevelopment. Negative associations between milk PCB and mental/motor development were reported at all ages, becoming significant from 30 months onwards. Over 30 months, for a PCB increase from 173 (5th percentile) to 679 ng/g lipids in milk (95th percentile) there was a decrease of 8.3 points (95% CI –16.5 to 0.0) in the Bayley Scales of Infant Development mental scores, and a 9.1 point decrease (95% CI –17.2 to –1.02) in the Bayley Scales of Infant Development motor scores. There was also a negative effect of postnatal PCB exposure via breastfeeding at 42 months using the Kaufman Assessment Battery. The study, published in the prestigious journal Lancet, demonstrates that prenatal and postnatal PCB exposures at current European background levels inhibits mental and motor development until 42 months of age and potentially beyond. .

Tatsuta et al. (2014) examined the associations between prenatal exposures to PCBs and intellectual ability using the Kaufman Assessment Battery for Children (K-ABC) at 42 months of age in the Tohoku Study of Child Development. Highly chlorinated PCBs were negatively correlated with the sequential and mental processing score of the K-ABC ($p<0.05$). There were no significant correlations between any K ABC score and either total Hg or lead. The negative effect of PCBs 206, 207, 208 remained even after adjusting for total Hg, lead, and other confounders. The K-ABC scores were significantly lower in the boys than in the girls. The authors concluded that the findings suggest that intellectual ability in the developmental stage may be impaired by prenatal exposures to highly chlorinated PCB congeners, especially in Japanese boys.

The Sapporo cohort study evaluate the effect of prenatal exposure to each PCB on child neurodevelopment at 6 and 18 months of age (Nakajima et al., 2017). Blood was collected in mothers after the second trimester of their last pregnancy and associations between maternal blood

PCB levels and the BSID-II scores for 6- and 18-month-old male children. Mono-ortho PCB isomers 114, 156, 157, 167, and 189 and total non-ortho PCB; and the WHO-05 total mono-ortho PCB TEQ, and total coplanar PCB TEQ, were all significantly negatively associated with the Psychomotor Developmental Index (PDI) at 6 months of age after adjustment for potential confounding variables. In a follow up of the Sapporo cohort study, total non-ortho PCBs were negatively associated with the Mental Processing Composite Score (MPCS) of K-ABC in males at 42 months of age (Ikeno et al., 2018). However, more optimal performance on cognitive tasks was found with higher prenatal PCB exposure in 1.5- and 3.5-year-old girls (not in boys) in the two studies from this Japanese cohort.

In a related study, Boucher et al., (2014) investigated the effects of prenatal exposure to PCBs on cognitive development, assessing different domains of cognition, in a sample of Inuit infants from Arctic Québec. Multiple regression analyses revealed that higher prenatal PCB exposure was associated with decreased Fagan Test of Infant Intelligence (FTII) novelty preference, indicating impaired visual recognition memory. This impairment of cognitive function already detected during the first year of life has long-term implications for cognitive development. These findings are consistent with previous reports based on study populations in Michigan; Taiwan; and Oswego, New York, that prenatal PCB exposure is related to impaired recognition memory on the FTII (Darvill et al. 2000; Jacobson et al. 1985; Ko et al. 1994), and extends this finding to the Inuit. Associations between prenatal PCB exposure and FTII novelty preference in three different cultures—the United States, Taiwan, and Nunavik—suggest a reliable and specific effect of prenatal PCB exposure on learning and memory that can already be detected in young infants.

In a prospective longitudinal study of Inuit children assessed at 11 years of age, Boucher et al. (2016) examined the relationship of pre- and postnatal exposure to PCBs, mercury and lead from sea mammals and fish consumption on fine motor functions. After adjustment for potential confounders and controlling for the other contaminants, higher current PCB concentrations were associated with poorer fine motor functions. Results were virtually identical when PCB153 was replaced by other PCB congeners. Higher current mercury levels were also independently associated with poorer function. Neuromotor impairments in fine motor speed appear particularly sensitive to postnatal PCB exposure.

Berghuis et al. (2013) assessed the impact of prenatal background exposures to PCBs and OH-PCBs on motor development in three-month –old infants from a Dutch cohort of 97 mother-infant pairs. Prenatal exposure to high background levels of most PCBs and 4-OH-PCB-107 seems to impair early motor development. Ruel et al. (2019) assessed the impact of PCBs on children's mental and motor development at 18 and 30 months of age in a Dutch cohort of 181 mother-infant pairs. The mental development index (MDI) and the motor development index (PDI) of the Bayley Scales of Infant Development II (BSID-II) was used to assess children′s mental and motor development (mean=100; delayed score<85). Higher prenatal PCB-153 levels were associated with a delayed MDI score at 18 months. Four OH-PCBs and the sum of 6 OHPCBs were positively associated with mental development at 30 months, whereas one OH-PCB was negatively associated at 18 months.

Some epidemiological studies, including a study by Gray et al. (2005) reported a lack of association between PCBs and IQ in the general US population. Stewart et al. (2012) examined two potential sources of inconsistency across studies: 1) confounding with non-PCB organochlorines and 2) the presence of negative confounding (i.e., suppressor variables). The former could confound PCBs and lead to spurious associations (Type I errors), while the latter could suppress PCB associations and obscure true associations (Type II errors). Results from Stewart et al. (2012) found that "placental PCB levels were associated with older mothers who were more educated and came from higher socioeconomic strata. Due to this fact, unadjusted relationships between PCBs and IQ appeared null or slightly positive. After control for confounders, several significant negative associations between PCBs and IQ were revealed. These data might suggest that inadequate control for confounders in PCB studies, where negative confounding is present, may bias results toward the null (Type II error) rather than spurious associations (Type I error)."

In recent studies, prenatal PCB exposure has not consistently been linked to less optimal performance on cognitive tasks in cohort studies assessing cognitive tasks in school age children (Zhang et al. 2017; Orenstein et al. 2014; Jacobson et al. 2015). However, Jacobson et al. (2015) stated that the failure to confirm previous evidence of PCB neurotoxicity in their study is likely attributable to exposure to a markedly less neurotoxic PCB congener mixture. The PCB exposure levels in the study by Orenstein et al. (2014) were also much lower than in most other cohorts that reported cognitive deficits. Similarly, the PCB levels in the serum of pregnant women in the HOME study of Zhang et al. (2017) were not elevated and similar to that in pregnant women in the general US population (National Health and Nutrition Examination Survey, 2003–2004; Woodruff et al., 2011).

Following a review of the most recent studies (published between 2014 -2018) Berghuisa and Roze (2019) concluded that prenatal exposure to PCBs interferes with normal child development, not only during the perinatal period, but up to adolescence. The effects of PCBs on neurodevelopmental outcomes are generally consistent throughout different studies, suggesting less optimal development after higher prenatal PCB exposure.

In summary, for approximately the past 30 years, a large number of epidemiological studies have consistently reported adverse neurodevelopmental outcomes associate with prenatal and/or postnatal environmental exposures to PCBs. Through measuring the relative magnitude of PCB exposure using biological specimens from study participants, it is possible to identify adverse outcomes that are associated with elevated PCB exposures within published studies. Together, the results of these studies and review articles clearly demonstrate that PCBs are neurotoxic and support the need to minimize PCB exposures in infants, young children, pregnant women, and women of childbearing age.

c. Behavioral Problems, including ADHD and Autism

A prospective longitudinal study in 196 children (mean age, 11.3 years) found that postnatal PCB exposure affects processes associated with error monitoring, an aspect of behavioral regulation required to adequately adapt to the changing demands of the environment (Boucher et al., 2012). This effect results in reduced task efficiency and may play a role in the PCB-related cognitive impairments reported in previous studies.

Behforooza et al. (2017) examined the relationship between current body burden of persistent PCBs and attention and impulsivity in 140 Akwesasne Mohawk young adults aged 17 to 21 whose environment has been contaminated by industrial effluent. Attention and impulsivity were measured by errors of omission, errors of commission, and patterns of reaction time responses on the Conners Continuous Performance Test. After adjusting for multiple covariates, regression analyses showed a significant positive relationship between PCB levels and omission scores, but only for males. The PCB levels of the adolescents in the Mohawk Adolescent Well-Being Study (MAWBS) (ages 10–16.9) were found to be negatively related to long-term memory (Newman et al., 2006, 2009) but were not found to be related to parent and teacher behavioral ratings of ADHD (Newman et al., 2014).

In a prospective birth cohort study conducted near a PCB-contaminated harbor in New Bedford, MA, higher PCB levels in umbilical cord predicted attention deficit/hyperactivity disorder (ADHD)–like behaviors reported by classroom teachers (Sagiv et al. 2010). In a subsequent study, Sagiv et al.(2012), assessed the association between cord serum PCBs and attention and impulse control in participants from a prospective cohort of 8 year old children born during 1993–1998 to mothers residing near a PCB-contaminated harbor in New Bedford. The results support an association between PCBs, and neuropsychological measures of inattention in boys.

Rosenquist et al. (2017) assessed the relationship between maternal prenatal and postnatal PCB-153 and behavior scores at 5–9 years of age among children in Greenland and Ukraine. Pooled adjusted odds ratios (ORs) for high conduct problem scores with a doubling of exposure were 1.19 (95% CI: 0.99, 1.42) and 1.16 (95% CI: 0.96, 1.41) for pre- and postnatal PCB-153, respectively. Corresponding ORs for high hyperactivity scores were 1.24 (95% CI: 0.94, 1.62) and 1.08 (95% CI: 0.81, 1.45) for pre- and postnatal PCB-153, respectively. The authors concluded that prenatal and early postnatal exposures to PCB-153 were associated with a higher, though not statistically significant prevalence of abnormal scores for conduct and hyperactivity at 5–9 years of age. In a related study, Kim et al. (2018) also reported that maternal blood PCB153 levels were higher among the children with behavioral problems, as indicated by the Child Behavior Checklist (CBCL).

These findings contribute to a growing literature showing associations between PCBs and children with behavioral problems and/or ADHD-related behavior.

Mechanistic studies by Wayman et al. (2012a,b), have shown that ryanodine receptor (RyR)-activation by PCB-95 (2,2´,3,5´6-pentachlorobiphenyl; a potent RyR potentiator) contributes to dynamic remodeling of dendritic architecture in cultured rat hippocampal neurons though a calcium-dependent signaling pathway responsible for activity-dependent dendritic growth. The authors conclude that PCBs are candidate environmental risk factors for neurodevelopmental disorders, especially in children with heritable deficits in calcium signaling associated with autism. In addition, Mitchell et al., 2012, found increased PCB-95 levels in post-mortem brain samples of subjects with 15q11-q13 duplication, a genetic form of autism.

Several recent epidemiological studies have found an association between PCB exposures and autism. Cheslack-Postava et al., (2013), found elevated, but not significant, odds ratios for

autism in children who had PCB and DDE levels above the 90th percentile of control values. In a larger study of this population, Brown et al. (2018) found no association between total levels of maternal PCBs and autism. The authors suggest that differences in the chemical mixtures and contexts of exposure between populations may explain inconsistencies in studies of PCBs and autism.

Lyall et al. (2017), reported that prenatal exposure to PCBs, as assessed by maternal mid-pregnancy serum PCB levels, increases offspring risk of autism spectrum disorder (ASD) and intellectual disability without autism (ID). The large population-based case–control study among Southern California births, included children with ASD (n = 545) meeting the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV-TR) criteria and ID (n = 181), as well as general population (GP) controls (n = 418). ASD risk was elevated for a number of PCB congeners, particularly for the highest vs. lowest quartile of PCB138/158 (adjusted odds ratios, AOR = 1.79; 95% CI: 1.10, 2.71) and PCB153 (AOR = 1.82; 95% CI: 1.10, 3.02). PCB138/158 was also associated with increased ID (AOR = 2.41; 95% CI: 1.18, 4.91), though no trend was suggested. These results suggest an increase in risk of ASD and ID with prenatal exposure to higher levels of PCBs. However, in an updated study using Bayesian analysis, Hamra et al. (2019) did not find evidence of an association between ASD or intellectual disability and exposure to PCBs.

Bernardo et al. (2019) examined the relation between plasma PCB concentrations measured during pregnancy and autistic behaviors in a subset of children aged 3–4 years old in the Maternal-Infant Research on Environmental Chemicals (MIREC) Study, a pregnancy and birth cohort of 546 mother-infant pairs from Canada (enrolled: 2008–2011). The study found no association between plasma PCB concentrations and autistic behaviors. However, a small increases in the mean Social Responsiveness Scale-2 (SRS) score and odds of more autistic behavior was found for the highest category of plasma PCB 138 concentrations compared with the lowest category, with an odds ratio of 1.8 (95% CI: 1.0, 2.9). The larger case-control study of Lyall et al. 2017 presented clearer evidence of monotonic dose-response relationships between PCBs (e.g., PCB 138 and 153) and risk of ASD in offspring. In addition to differences in statistical methodology, differences in mixtures to which study populations are exposed (for example, other chemicals acting as confounders, or dietary factors that modify associations) could also account for discrepancies across existing work.

Other studies have not reported an association of autism with PCB exposures. For example, Nowack et al. (2015), assessed the association between maternal blood PCB levels during pregnancy with autistic traits in their children at 10 years of age using the Social Responsiveness Scale (SRS; n = 100). In all participants, PCB levels were negatively associated with the Autistic Mannerisms subscale score, and in girls, PCB levels were negatively associated with the Social Cognition and Autistic Mannerisms subscale scores. While Nowack et al. (2015) reported better performance in children with greater exposures to PCBs, the authors suggested that this may be due to the low level of PCB exposure in their study participants relative to other cohort studies. Recently, Forns et al. (2018) pooled seven European birth cohort studies encompassing 4437 mother– child pairs from the general population to assess the association of PCB-153, p-p_-DDE and HCB measured in cord blood, maternal blood or milk with ADHD in childhood. In the largest study to date, the authors did not observe any association between either pre- or postnatal

exposure (up to 24 months) to PCB-153, p-p_-DDE and HCB and the risk of ADHD before the age of 10 years.

While there remains a lack of consistency in associations of autism with PCB exposures, most of the developmental studies provide support for the importance of minimizing PCB exposures to young children, pregnant women and to women of childbearing age.

d. Auditory Function

Two early studies of the association between PCB exposure and measures of hearing in children have produced mixed results. For example, among participants in the Collaborative Perinatal Project, maternal PCB concentration in pregnancy was not associated with sensorineural hearing loss at 8 years of age (Longnecker et al. 2004). In contrast to these null results, higher cord blood PCB concentrations were associated with a higher hearing threshold (hearing deficit) on audiometry at 7 years of age in a cohort of children in the Faroe Islands (Grandjean et al. 2001). Although both of these studies focused on *in utero* exposure to PCBs, studies of children and adolescents living in a highly polluted area of eastern Slovakia showed consistent adverse associations between PCB concentrations measured concurrently with otoacoustic emissions (OAEs; hearing deficits) during childhood (Trnovec et al. 2008, 2010).

Jusko et al. (2014), investigated the association between pre- and postnatal PCB concentrations in relation to cochlear status, assessed by distortion product otoacoustic emissions (DPOAEs), as a measure of ototoxicity in a cohort of children in eastern Slovakia. Maternal and cord PCB-153 concentrations were not associated with DPOAEs at 45 months, while higher postnatal (child blood) PCB concentrations at 6-, 16-, and 45-months of age were associated with lower (poorer) DPOAE amplitudes. The finding of this study provide an important example of postnatal rather than maternal or cord PCB concentrations (exposures) being the sensitive time period associated with poorer performance on otoacoustic tests at age 45 months. While Sisto et al. (2015) confirmed the deficits in hearing with elevated serum PCB 153 concentrations in children (postnatal exposure), they found improved DPOAEs at 45 months with cord blood PCB 153 (prenatal exposure). In addition, they found similar effects with exposure to organochlorine pesticides. Importantly, Palkovicova Murinova et al. 2016, followed up this cohort and found that the DPOAE-child serum PCB correlation obtained at 72 months of age is similar to that at 45 months suggesting a permanent and stable ototoxic effect of the PCB exposure in children.

Together, these studies demonstrate the association of PCB exposures with deficits in hearing in children and provide further support for minimizing PCB exposures to young children, pregnant women and to women of childbearing age.

e. Other Developmental Effects in Humans Exposed to PCBs

Jan and Vrbic (2000) and Jan et al. (2007) evaluated 432 Slovenian children 8 – 9 years of age for PCB exposures and developmental dental defects. This study found a dose-response

relationship between PCB exposure and developmental enamel defects of permanent teeth in children.

Hansen et al. (2014) investigate the association between maternal serum concentrations of PCBs, HCB, and *p,p´*-DDE in a cohort of environmentally exposed Danish pregnant women and risk of asthma in offspring after 20 years of follow-up. Maternal serum concentrations of HCB and dioxin-like PCB-118 were positively associated with offspring asthma medication use after 20 years of follow-up (p for trend < 0.05). Compared with subjects in the first tertile of maternal concentration, those in the third tertile of PCB-118 had an adjusted hazard ratio (HR) of 1.90 (95% CI: 1.12, 3.23). Weak positive associations were also estimated for PCB-156 and the non-dioxin-like PCBs (PCBs 138, 153, 170, 180). The results support the conclusion that maternal concentrations of PCB-118 and HCB were associated with increased risk of asthma in offspring followed through 20 years of age.

2. Neurotoxic Effects in Adult Humans Exposed to PCBs

The adverse impact of PCBs on cognitive function was also found in a study of former PCB-exposed workers of a transformer and capacitor recycling company in Germany, their family members, employees of surrounding companies and area residents (Fimm et al., 2017). Adults with increased plasma levels of PCBs 28, 52, 101 following occupational exposure showed reduced verbal fluency and a stronger decline of word production with time-on-task. In addition, increased levels of PCBs 138, 153, 180 and dioxin like PCBs (77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169, 189) correlated with reduced fine motor function in Aiming and Line Tracking. Other cognitive functions such as memory, cognitive flexibility, intrinsic alertness, reasoning, and working memory were not affected.

Fitzgerald et al. (2008) evaluated neuropsychological status and low-level PCB exposure among older adults (55 and 74 years of age) living along contaminated portions of the upper Hudson River in New York. After adjustment for potential confounders, the results indicated that an increase in serum total PCB concentration from 250 to 500 ppb (lipid basis) was associated with a 6.2% decrease in verbal learning, as measured by California Verbal Learning Test trial 1 score (p =0.035), and with a 19.2% increase in depressive symptoms, as measured by the Beck Depression Inventory ($p = 0.007$). The authors conclude that the results suggest that exposure to PCBs may be associated with some measures of memory and learning and depression among adults 55–74 years of age whose current body burdens are similar to those of the general population.

To investigate the impact of PCB exposure in older adults, Bouchard et al. (2014) examined the cross-sectional association between serum PCB concentrations and cognitive function in older adults (60 to 84 years of age) from the general U.S. population, consisting of 708 respondents, 60–84 years of age, participating in the National Health and Nutrition Examination Survey (1999–2002). Cognitive function was assessed with the Digit-Symbol Coding test, adjusting the analyses for age, education, race/ethnicity, and poverty/income ratio. The findings suggest that PCB neurotoxicity may contribute to cognitive deficits in older persons at low levels found in the general U.S. population.

Consistent findings are related to depression and depressive symptoms after occupational (Gaum et al., 2014; Kilburn et al., 1989), as well as environmental PCB exposure (Fitzgerald et al., 2008). Although Seegal et al. (2013) report no correlation between PCBs and trait anxiety and depressive symptoms in former capacitor workers, Fitzgerald et al. (2008) report a strong positive correlation between PCB body burden and depressive symptoms in elderly PCB exposed Hudson River residents. Similarly, in a longitudinal study, Gaum et al. (2014) found a higher risk for depressive syndrome in individuals with occupational exposures to PCBs over a period of three years. Recently, Gaum et al. (2017) conducted a cross-sectional and longitudinal investigation of depression in the German HELPcB surveillance program (Health Effects in high Level exposure to PCB) for occupationally exposed workers and their relatives. They found that PCB body burden is associated with more depressive symptoms and lower urinary concentrations of the dopamine metabolite, homovanillic acid (HVA) as a surrogate for dopamine. Furthermore, Gaum et al. (2019) found an interaction effect between lower chlorinated PCB exposure and free thyroxin (fT4) related to the main dopamine metabolite HVA, as well as related to depressive symptoms. These finding suggest that depressive symptoms associated with PCB exposures may be mediated by alterations in the thyroid and dopamine system over time.

3. Importance of ryanodine receptor (RyR) activators in Neurotoxicity of PCBs: Example of PCB 95

Altered patterns of dendritic growth and plasticity are associated with impaired behavior in experimental models (Berger-Sweeney and Hohmann 1997) and contribute to diverse neurodevelopmental disorders (Pardo and Eberhart 2007; Zoghbi 2003), suggesting the possibility that PCBs elicit developmental neurotoxic effects by interfering with neuronal connectivity. Yang et al. (2009) reported that developmental exposure to Aroclor 1254 interferes with normal patterns of brain dendritic growth and plasticity, and these effects may be linked to changes in RyR expression and function. In addition, developmental exposure to PCB 95 or Aroclor 1254 impaired cognitive behavior in weanling rats at doses that enhance neuronal connectivity *in vivo* with increased brain dendritic growth (Kenet et al., 2007; Yang et al., 2009). In extending the importance of these experimental results to humans, Mitchell et al., (2012) recently reported that PCB 95, but not other PCBs or PBDEs, are significantly higher in postmortem brains of children with a syndromic form of autism, compared with controls. Significantly, Lesiak et al. (2014), made the important observation that exceeding low concentrations of PCB 95 (~6.5 ng/g) were observed to increase development of dendritic spines in cultured hippocampal neurons, and that this concentration is comparable to the levels of PCB 95 detected in the brains of autistic children (3–15 ng/g) (Mitchell et al., 2012). Potentially even lower levels of exposure to NDL PCBs might adversely influence neuronal connectivity in the developing brain of genetically susceptible individuals. PCB-95 modulates the calcium-dependent signaling pathway and promotes dendritic growth via ryanodine receptor-dependent mechanisms (Wayman et al., 2012a, 2012b). The authors conclude that PCBs, particularly *ortho*-substituted PCBs with high RyR activity are risk factors in neurodevelopmental disorders.

Simon et al. (2007) acknowledged the well-known neurotoxic effects of PCBs and proposed and developed an initial relative potency scheme for non-dioxin like PCBs, referred to as the Neurotoxic Equivalent (NEQ) scheme. The NEQ scheme is based on the modes of action for diortho-PCB congeners, including ryanodine receptor (RyR)-activation resulting in interference with intracellular signaling pathways that are dependent on Ca2+ homeostasis and the

consequent cellular, organ-level and organismal effects. These non-coplanar PCB congeners produce other adverse effects including changes in protein kinase C translocation, changes in cellular dopamine (DA) uptake, and formation of reactive oxygen species. These endpoints may be related by similar cellular or biochemical mechanisms, or the endpoints related to the neurotoxic activity of PCBs.

4. Reproductive Dysfunction in Humans Exposed to PCBs

Exposure to PCBs has long been associated with reproductive dysfunction in humans, including decreased sperm motility (Meeker et al., 2010), decrease in fecundity (Faroon et al., 2001), earlier menarche (Schell et al., 2010), altered sex ratio (Karmaus et al., 2002; Timmermann et al., 2017), and altered gonadal hormones in newborns (Cao et al., 2008). Epidemiological studies have also focused on the effects of developmental exposure on adult physiological function. As in newborns, greater concentrations of serum NDL PCBs was associated with reduced testosterone in adolescent (PCB 138 153, 180) and adult (PCB74, 99, 153, and 206) males (Goncharov et al., 2009; Grandjean et al., 2012). After adjusting for age, BMI, total serum lipids, and concentrations of 3 pesticides (HCB, DDE, and mirex), Goncharov al. (2009), found that a reduction in circulating serum testosterone levels in adult male Native Americans was associated with serum concentrations of total PCBs, four single PCB congeners, and four PCB congener groups (mono-ortho, di-ortho, tri-tetra-ortho, and dioxin-like). Concentrations of eight other PCB congeners, one congener group, and three pesticides were not correlated with testosterone concentration. Although serum testosterone levels were not outside of the normal reference range, the findings clearly demonstrate that PCBs alter endocrine function.

Exposure to specific congeners, as measured in the blood of mothers immediately following parturition, also affected time to pregnancy in daughters. Specifically, higher levels of PCBs 187, 156 and 99 were associated with longer time to pregnancy, while higher levels of PCBs 105, 138 and 183 was associated with shorter time to pregnancy (Cohn et al., 2011).

Meeker et al. (2011) investigated the relationship between serum PCB concentrations and early pregnancy loss among women undergoing in vitro fertilization (IVF). PCB-153 and the sum of all measured PCB congeners (ΣPCBs) were associated with significantly elevated dose-dependent odds of failed implantation. The odds of failed implantation were doubled, and the odds of a live birth were reduced by 41%, among women in the highest serum PCB-153 quartile compared with women in the lowest PCB-153 quartile. Serum ΣPCBs, which was strongly correlated with PCB-153, was also associated with implantation failure and reduced odds of a live birth. In conclusion, they found that serum PCB concentrations representative of those measured among the U.S. general population were associated with increased odds of failed implantation among women undergoing IVF. These findings may help explain previous reports of reduced fecundability and increased time to pregnancy among women exposed to PCBs (Axmon et al 2006; Buck et al. 2000, 2009).

A related prospective study assessed the correlation between PCBs 28, 52, 138, 180 in the follicular fluid (FF) obtained during intracytoplasmic sperm injection (ICSI) with the ovarian response, endometrial thickness, and embryological and clinical outcomes (Al-Hussaini et al., 2018). Higher concentrations of PCBs are associated with thinner endometrial thickness. The

higher the level of PCB 28 and 180, the lower the retrieval, fertilization, and embryo cleavage rates.

Bloom et al. (2017) reported further evidence supporting the adverse effect of PCBs, in ovarian follicular fluid, on in vitro fertilization (IVF). The pilot study found significant inverse associations between higher levels of PCB congeners and indicators of ovarian reserve (e.g., antral follicle count), follicular response to administered gonadotropins (e.g., peak estradiol, number of oocytes retrieved, endometrial thickness), intermediate IVF endpoints (e.g., oocyte fertilization and embryo quality), and clinical IVF outcomes (embryo implantation and live birth), after adjusting for body mass index, cigarette smoking, race, and age.

Buck Louis et al. (2013) examined the relationship between PCBs and couple fecundity as measured by time to pregnancy. In this couple-based prospective cohort study with preconception enrollment and quantification of exposures in both female and male partners, they observed that several PCB congeners were associated with reduced fecundity (PCBs 118, 167, 209 for females, and PCBs 138, 156, 157, 167, 170, 172, and 209 for males). In a related study, Han et al. 2016, reported decreased fecundability in female offspring of Michigan fish eaters was found to be associated with PCB exposure in utero, possibly related to endocrine disruption in the oocyte and/or other developing organs influencing reproductive capacity in adulthood.

Gallo et al. (2016), assessed the impact of serum PCB levels on menstrual cycles and ovulatory status, determined by saliva estradiol and progesterone levels, in an Akwesasne Mohawk population in upstate NY. While no association was observed with the levels of persistent PCBs, for every unit increase in levels of ΣMonoOrthoPCBs20% there was a 2.4 times greater likelihood of a woman experiencing a non-ovulatory cycle controlling for individual differences in age, BMI, parity, and cigarette and alcohol use. The finding of an association of ovulatory status with mono-ortho PCBs, especially PCBs 28 and 66, suggests the risk of ongoing airborne, inhalation exposures to these PCB congeners.

Most recently, Gallo et al. (2018) examined the association of PCBs on menstrual cycle day 3 follicle stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E2) levels in a sample of women from the Akwesasne Mohawk Nation with known exposure due to local environmental pollution. For every unit (ppb) increase in the serum level of the estrogenic PCB group, there was a 5-fold greater risk of an elevated FSH:LH ratio (≥ 2), controlling for individual differences in age, percent body fat, cycle day 3 estradiol levels, parity, alcohol use and cigarette smoking in the past year. Elevated cycle day 3 FSH levels are associated with decreased oocyte quality, quantity, and fertility response. It is important to note that the reduced ovarian responsivity (elevated FSH:LH ratio) was specific to PBCs, and not associate with p,p′ -DDE and HCB. Unwanted inhalation exposure to PCBs, including estrogenic PCBs, can occur when they become airborne when they volatilize from dredged PCB-contaminated soil or from indoor PCB-containing older buildings. The authors conclude that PCB exposure, particularly to non-persistent, estrogenic congeners, may pose an unrecognized threat to female fecundity within the general population.

Earlier, Petro et al. (2012) also found that elevated ovarian follicular PCB levels significantly reduced fertilization rate and reduced the proportion of high-quality embryos relative

to the amount of retrieved oocytes, even when the analysis is adjusted for age, estradiol concentration, BMI, fertilization procedure and male subfertility as explanatory variables.

Tang et al. (2018) conducted a cross-sectional study to analyze the associations between PCB levels in umbilical cord serum and reproductive hormones and birth outcomes of mothers and newborns. Follicle-stimulating hormone (FSH) was decreased by all PCB congeners and reached statistical significance with PCB 101. Luteinizing hormone (LH) was decreased by all PCBs (except 180) and reached statistical significance with PCB 52. Testosterone (T) was deceased by all PCBs (except 138) and reached statistical significance with PCB 28 in all newborns and PCB 118 in males only. Head circumference was decreased by all PCBs (except 138) and reached statistical significance for PCBs 101 and 118. Gestational age was reduced by most PCBs and reached statistical significance with PCBs 28 and 101. Thus, PCBs in umbilical cord blood are negatively associated with reproductive hormone levels and negatively affect birth outcomes.

Environmental exposures to PCBs have been associated with decreased semen quality, a key indicator of male reproductive health. Hauser et al. (2003), presented evidence of an inverse dose–response relationship between PCB-138 and sperm concentration, motility, and morphology. McAuliffe et al. (2012) conducted an epidemiologic study to investigate the relationship between environmental exposure to PCBs and sperm sex chromosome disomy (two copies of a chromosome). Men with higher serum levels of PCBs had significant increases in the rates of YY, XY, and total sex-chromosome disomy, after adjustment for potential confounders.

In a case-control study of serum PCBs and semen parameters serum mono-ortho PCBs and non-ortho PCBs were significantly higher in the low semen quality group than in the normal semen quality group and elevated PCB 126 was associated with reduced sperm viability in men with low semen quality (Paul et al., 2017). Multivariate regression models were created with continuous semen parameters (semen volume, sperm concentration, sperm total count, sperm progressive motility, sperm viability and normal morphology) as dependent variables and DL-PCBs as the predictor or independent variables. When the data from the overall group ($n = 50$) were analyzed, a statistically significant negative correlation of sperm progressive motility was found for PCB 126 and 189 and that progressive motility was reduced, but did not reach the level of statistical significance, for 9 of 10 other PCB congeners and 3 of 3 PCB groups. A highly significant relationship between reduced sperm viability was found with PCB 126 ($p = 0.001$), PCB 169 ($p = 0.002$), PCB 189 ($p < 0.001$), non-ortho PCBs ($p = 0.004$) and total levels of DL-PCBs, and viability was reduced, but did not reach the level of statistical significance, for 7 of 9 other PCB congeners and mono-ortho PCBs. No consistent relationship was found for sperm morphology, which was positively correlated with PCB123 but negatively correlated with PCB 189. Notably, although not reaching the level of statistical significance, sperm concentration and total sperm count were consistently reduced with 11 of 12 PCB congeners and in 3 of 3 PCB groups. Based on the results of this study, Paul et al., (2017) concluded that, “Clinicians should consider evaluating DL-PCB congener profiles in the comprehensive study of male partners from couples with unexplained infertility even in those subjects with normal semen quality.”

In a large prospective birth cohort in the Faroe Islands of 2,152 healthy mother– child pairs, a doubling in total PCBs in maternal serum or umbilical cord blood was associated with an increased odds by 8% (95% CI = 0–16%) of giving birth to a boy (Timmermann et al., 2017). The

authors combined cohorts, resulting in greater power, and adjusted the analysis for cohort, maternal parity and maternal age. Thus higher prenatal exposure to PCBs was associated with an increased secondary sex ratios in a population with a tradition for high consumption of marine food and high serum concentrations of PCB.

Epidemiological evidence have found that PCBs are highly concentrated in serum, peritoneal fluid and adipose tissue in patients with endometriosis (Porpora et al., 2009). Data from Italy showed that serum concentration of PCBs in patients with endometriosis was 410 ± 220 ng/g, lipid bases, and 250 ± 140 ng/g in non-endometriosis patients (Porpora et al., 2006). A case control study found significant associations between deep infiltrating endometriosis (DIE) and adipose tissue levels of PCB 105, 114, 118 and 123 using unconditional logistic regression adjusted for known confounding variables, including age and BMI (Ploteau et al., 2017). Several population-based studies have proposed that exposure to PCBs may increase the risk of developing endometriosis, while some epidemiological studies have failed to find any association between PCBs and endometriosis (reviewed by Yao et al., 2017). Thus, the relationship between exposure to PCBs and different patterns of endometriosis remains controversial.

Together, these studies demonstrate the association of PCB exposures with reproductive dysfunction in humans and provide further support for minimizing PCB exposures.

5. Pubertal Developmental Effects in Humans Exposed to PCBs

Brucker-Davis et al. (2008) conducted a prospective case-control study to assess the incidence of cryptorchidism in male children exposed to PCBs during prenatal and postnatal life. Study results suggested a positive association ($p = 0.045$) between high total PCB concentrations in human milk (perinatal exposure) and cryptorchidism in boys.

Denham et al. (2005) studied a cohort of 138 girls (10-16.9 years old) from the Akwesasne Mohawk Nation, Franklin County, New York USA, who had been exposed to PCBs via food. They compared blood PCB levels against attainment of menses. The geometric mean (0.12 ppb) of estrogenic PCBs (PCB 52, 70, 90/101, 187) was associated with a significantly greater probability of having started menarche early ($\beta = 2.12$). The study suggested that even at low levels of estrogenic PCBs, the time to menarche attainment decreased.

The sum of 16 PCB congeners (Σ16PCBs) that were detected in ≥ 50% of Akwesasne Mohawk males, 10 to < 17 years of age, was significantly and negatively associated with serum testosterone levels, such that a 10% change in exposure was associated with a 5.6% decrease in testosterone (95% CI: –10.8, –0.5%) (Schell et al., 2014). Dichlorodiphenyldichloroethylene (*p,p´*-DDE), was positively but not significantly associated with serum testosterone (5.2% increase with a 10% increase in exposure; 95% CI: –0.5, 10.9%). Neither lead nor hexachlorobenzene (HCB) was significantly associated with testosterone levels. Thus the endocrine disruption, resulting in reduced serum testosterone levels, was only associated with environmental exposures to PCBs and not with other common environmental contaminants.

In a longitudinal cohort of 473 Russian boys, Korrick et al. (2011) found that baseline levels of non-dioxin-like PCBs in boy at 8 – 9 years of age were associated with an earlier pubertal onset as assessed by testicular volume at age 12, while TEQ levels were associate with later pubertal onset. Higher maternal serum non-dioxin-like PCBs, measured when the boys were age 8–9 years, were also associated with earlier pubertal onset among boys (Humblet et al. 2011). These findings suggest that maternal ΣPCB serum concentrations collected 8 or 9 years after their sons' births, which may reflect their sons' prenatal and early-life exposures, are associated with acceleration in some measures of pubertal onset, specifically genital staging. This association was not attenuated by adjusting for multiple covariates including the son's peripubertal serum concentration of ΣPCBs and TEQs. A prospective follow up of this cohort through ages 17–18 years continued to find that TEQs delay, while non-dioxin-like PCBs advance, the timing of male puberty (Burns et al. 2016). The highest quartile of Σnon-dioxin-like PCBs compared with the lowest was significantly associated with earlier sexual maturity by testicular volume and genitalia. In multiple organochlorine models adjusted for baseline height and BMI *z*-scores, the associations of Σnon-dioxin-like PCBs with earlier pubertal onset were strengthened.

In related studies, smaller longitudinal studies of 244 U.S. boys (Gladen et al. 2000) and 60 Taiwanese boys (Hsu et al. 2005) assessed prenatal serum non-dioxin-like PCB concentrations and did not find associations with timing of male pubertal development. Cross-sectional Belgian studies also examined the association of peripubertal serum non-dioxin-like PCB (PCBs 138, 153, and 180) concentrations with male pubertal development by Tanner staging. Although the initial study found later pubertal development with higher serum non-dioxin-like PCBs among 80 boys (Den Hond et al. 2002), subsequently a much larger study (n = 887) reported a doubling of serum non-dioxin-like PCBs associated with earlier puberty (Den Hond et al. 2011). The study by Den Hond et al. (2011) in 14- to 15-year-old Flemish adolescents found that the sum of PCBs 138, 153 and 180 were significantly and positively associated with earlier pubertal development in boys, both with genital and pubic hair development. Higher NDL-PCBs in boys was also associated with higher serum testosterone and lower estradiol, supporting the anti-estrogenic activity of PCBs (Croes et al., 2014).

Together, these studies suggest that exposure to certain PCB congeners may interfere with sexual maturation and has implications for both adolescent and adult health.

6. Liver Injury in Humans Exposed to PCBs

Liver injury has been associated with PCB exposure in laboratory animals and humans. A wide range of responses have been observed in laboratory animals exposed to PCBs, including, microsomal enzyme induction, liver enlargement, increased serum levels of liver enzymes and lipids, and histopathological alterations that progress to fatty and necrotic lesions and tumors (Treon et al. 1956; Bruckner et al. 1973; Lecavalier et al., 1997; Allen et al. 1974; Tryphonas et al. 1986; Arnold et al. 1993, 1997; Norback and Weltman 1985; ATSDR 2000). Human studies of occupational exposure to PCBs have reported elevated serum levels of liver enzymes (gamma-glutamyl transpeptidase, GPT; alanine aminotransferase, ALT; aspartate aminotransferase, AST; alkaline phosphatase, AP: and/or lactate dehydrogenase, LDH), triglycerides and cholesterol. An increase in serum liver enzymes, indicative of liver injury, was found in a number of studies to be

directly related to an increase in serum PCB levels (Baker et al. 1980; Chase et al. 1982; Emmett et al. 1988; Fischbein 1985; Fischbein et al. 1979; Lawton et al. 1985; Smith et al. 1982). Alvares et al. 1977, reported that occupational exposure to PCBs was associated with an increase in the rate of metabolism of antipyrine (an analgesic), indicating the induction of drug metabolizing enzymes. Occupational exposure to PCBs has also been reported to produce hepatomegaly (liver enlargement) and an elevation of serum levels of liver enzymes (Maroni et al. 1981). Additionally, occupational exposure to PCBs has been shown to be associated with an increase in urinary excretion of total porphyrins and porphyrin homologues (coproporphyrin, pentaporphyrin, hexaporphyrin, heptaporphyrin, and uroporphyrin) (Colombi et al. 1982). Hepatic dysfunction, consisting of elevated serum triglycerides and liver enzymes (transaminases and alkaline phosphatase) and elevated urinary uroporphyrins were reported in the Yusho and Yu-Cheng incidents (Kuratsune 1989; Rogan 1989). The Yusho incident occurred in 1968 in Japan, due to an accidental, relatively short-term exposure of humans to rice oil contaminated by PCBs. A similar incident, referred to as Yu-Cheng, occurred 11 years later in Taiwan. Mortality from cirrhosis of the liver and from liver diseases excluding cirrhosis was also increased in Yu-Cheng victims during a 12 year period following exposure (Hsieh et al. 1996). Environmental exposure of residents of Triana, Alabama to contaminated fish also found elevated serum PCBs correlated with an elevation of serum ALT and cholesterol (Kreiss et al. 1981). All of the above studies support the association of PCB exposure with liver injury.

More recently, Cave et al. (2010) investigated the association of serum PCBs with an elevation in serum alanine aminotransferase (ALT) activity and suspected nonalcoholic fatty liver disease (NAFLD) in the general U.S. adult population (NHANES 2003–2004 adult participants). PCBs were associated with dose-dependent increased adjusted ORs for ALT elevation. In addition, an increase in lipid-adjusted serum levels of 20 PCBs were individually associated with ALT elevation. These results suggest a possible association between low-level environmental PCB exposure and the development of liver disease and suspected NAFLD.

Several more recent epidemiological studies have assessed the association of low level, general background levels of PCBs and markers of liver injury. Serum PCBs were positively correlated with liver toxicity markers [serum aspartate transaminase (AST), alanine transaminase (ALT), and γ-glutamyltransferase (γGT)], independently of age and body mass index (Kim et al., 2011). In a related study, serum markers of liver dysfunction were positively associated with PCBs in 992 individuals (all aged 70 year) using a regression model adjusted for sex, kidney function, smoking, body mass index, waist circumference, blood glucose, systolic blood pressure, exercise habits, education and medication (Kumar et al., 2014). Kumar et al. (2014) found significant increases in serum bilirubin with PCBs 105, 118, 126, alanine transaminase (ALT) with PCBs 74, 99, 105, 118, and alkaline phosphatase (ALP) with PCBs 126. All of these are serum markers of liver injury in this population which has general background levels of exposure to PCBs. In a cross-sectional assessment of the NHANES 2003-2004 data, elevated liver enzymes (ALT, AST, and GGT) were consistently found in the highest group of DL PCBs when compared to the lowest exposure group, although the effects on liver enzymes are within normal clinical ranges (Serdar et al., 2014). In another analysis of these data, the significant role of PCBs in elevating markers of liver injury was confirmed using a linear regression models were constructed for each chemical separately, then as a class, using quartiles to represent exposure and adjusting for age, sex, race, income, and BMI (Yorita Christensen et al., 2013).

A recent, more mechanistic, study of liver disease utilized the Anniston Community Health Survey (ACHS), a PCB-exposed residential cohort previously found to have a high prevalence of overweight/obesity and diabetes (Silverstone et al., 2012). Clair et al. (2018) found a high prevalence of biomarker indicated liver disease in 60.2% of the cohort and characterized 80.7% of these cases as toxicant-associated steatohepatitis (TASH) which was characterized by predominant hepatocellular necrosis. TASH was associated with increased exposures to ortho-substituted PCB congeners, dyslipidemia, insulin resistance, and proinflammatory cytokine elevations consistent with PCB related steatohepatitis (a type of fatty liver disease, characterized by inflammation of the liver with concurrent fat accumulation in liver). PCBs were associated with decreased pancreatic insulin production and the diabetes previously associated with PCB exposures may be related to the combination of decreased pancreatic insulin production and increased insulin resistance due to PCB-related TASH.

The consistency of these studies is noteworthy and suggests that PCBs contribute to liver injury in the general population. This is especially of concern due to the prevalence of alcohol-induced liver injury in the general population, such that additional injury caused by PCBs could be especially harmful.

7. Endocrine Disruption in Humans Exposed to PCBs

a. Diabetes

Epidemiological studies suggested that exposure to low concentrations of polychlorinated biphenyls (PCBs) similar to current exposure levels in humans increases diabetes risk. Multiple cross-sectional analyses of National Health and Nutrition Examination Survey (NHANES) cohorts from 1999–2006 found concentrations of PCB-170 in blood consistently associated with type 2 diabetes (T2D) with significant adjusted odds ratios of 2.3 and 4.5 in 1999-2000 and 2003-2004 cohorts, respectively (Patel et al. 2010). Wu et al. 2013, prospectively examined plasma PCB concentrations in relation to incident T2D and summarized existing evidence in a meta-analysis. After pooling results with those of six published prospective studies that included 842 diabetes cases in total, PCBs were associated with diabetes, pooled ORs 1.70 (95% CI: 1.28, 2.27). Song et at. 2015 conducted a recent comprehensive review of the published literature on PCBs and the risk of type 2 diabetes and diabetes related metabolic traits. PCB studies included 20,336 participants from 19 cross-sectional populations and 4,681 from seven prospective cohorts with follow-up periods of 5–25 years. In both cross-sectional and prospective studies, serum PCB concentrations (including different PCB congeners) were significantly associated with higher risk of type 2 diabetes. PCB concentrations were also associated with higher fasting glucose. In another recent review, Tang et al., (2014) found similar consistent findings of an association of PCBs and type 2 diabetes. Twenty three peer reviewed scientific articles were evaluated in the meta-analysis which found quantitative evidence supporting the conclusion that exposure to PCBs is associated with an increased risk of incidence of type 2 diabetes. Silverstone et al. (2012) conducted a cross-sectional study of randomly selected households and adults who lived near the Monsanto plant that manufactured PCBs in Anniston, AL who underwent measurements of height, weight, fasting glucose, lipid, and PCB congener levels and verification of medications. After adjusting for diabetes risk factors, the study demonstrated a statistically significant association of serum PCB levels with increased diabetes prevalence overall, especially among women. In participants < 55 years of age, the adjusted OR for diabetes for the highest versus lowest quintile

was 4.78 (95% CI: 1.11, 20.6), supporting the observation that the disease developed at an earlier age of onset with PCB exposure. Recently, Aminov et al., 2016, assessed the association of PCB congeners and congener groups on the prevalence of diabetes in 601 Akwesasne Native Americans. When comparing highest to lowest quartiles only non- and mono-*ortho* PCBs 1, 3, 13, 15, 7, 9, 6, 8, 29, 26, 25, 31, 28, 33, 22, 67, 63, 74, 70, 66, 56, 77, 118, 114, 105, 156 [OR = 4.55 (95% CI: 1.48, 13.95)], tri- and tetrachloro PCBs 19, 18, 17, 24+27, 32+16; 29, 26, 25, 31, 28, 33, 53, 51, 22, 45, 46, 52, 49, 47+59, 44, 42, 71, 64, 40, 67, 63, 74, 70, 66, 56, 77 [OR = 3.66 (95% CI: 1.37, –9.78)] and HCB, hexachlorobenzene [OR = 2.64 (95% CI: 1.05, 6.61)] showed significant associations with diabetes. Aminov et al. (2016) acknowledged that the concentrations of many of these congeners were below the method detection limits (MDLs) in a significant number of the subjects, so a subset of the analyses was done after deleting all non-dioxin-like congeners for which 40% or more values were below the MDL. Under these condition (analyzing only PCB congeners detected in most participants), the associations between prevalence of diabetes and quartiles of non-dioxin like PCB congeners were highly significant in the highest quartile which had an OR of 3.53 (1.26-9.89, 95% CI), p = 0.016, when adjusted for total pesticides as well as age, gender, BMI, and serum concentrations of total lipids. The associations with diabetes after adjustment for other persistent organic pollutants (POPs) were strongest with the more volatile, non-dioxin-like, low-chlorinated PCB congeners and HCBs, suggesting that inhalation of vapor-phase PCBs is an important route of exposure.

A few studies that have not reported an association between PCBs and diabetes. Zani et al. (2013a) reported that diabetes frequency increased according to the serum concentrations of total PCBs and single PCB congeners, but no association was found when estimates were adjusted for education, body mass index, age and gender by logistic regression analysis. This study is limited by a relatively small number of subjects with diabetes, which is not unexpected since a random sample of the general adult population was included in the study, most of whom were healthy. In the samples, the diabetes percentage was 12.9% in males and 7.3% in females, in agreement with national data (10% in males and 7% in females). Turyk et al. (2009) found that dioxin-like PCBs were associated with diabetes in Great Lakes fish consumers, although the association was not independent of DDE exposure. The authors also note that omega 3 fatty acids from fish consumption could potentially be protective for diabetes. In addition, the authors acknowledged that they underestimated total dioxin-like PCB exposure by measuring only selected dioxin-like mono-ortho PCB congeners (sum of PCBs 118 and 167) , which could have biased the findings to the null hypothesis**.**

Zong et al. (2018) conducted a nested case-control study investigating the association between plasma PCB concentrations in the late 1990s and incident type 2 diabetes (T2D) over 11 years of follow-up in the Nurses' Health Study II. For 793 case–control pairs of T2D, using a multiviarate-adjusted model, total dioxin-like PCBs (5 mono-ortho congeners, PCB-105, 118, 156, 157, and 167) had an OR of 1.95 (95% CI, 1.42 - 2.69; p for trend < 0.001). Adjustment for previous weight change and body mass index (BMI) at blood draw attenuated these associations, but the association of T2D for DL-PCBs remained significant with an OR of 1.78 (95% CI, 1.14 - 2.76]; p for trend = 0.006).

Zhang et al. (2018) conducted a prospective study with a nested case-control design to determine the association of PCB exposure in early pregnancy with gestational diabetes mellitus.

They found that serum levels of specific non-dioxin-like PCBs in early pregnancy disturb the glucose metabolism and increase the risk of gestational diabetes mellitus. The odds ratios (OR) of PCB-28, PCB-52, and PCB-101 for gestational diabetes mellitus were 1.86 (95% CI: 1.05–3.27), 1.90 (95% CI: 1.28–2.82) and 1.85 (95% CI: 1.22–2.82), respectively. However, after adjusting for confounders (BMI, total lipids) including some PCB congeners, only PCB-52 remained significantly associated with GDM with OR of 1.97 (95% CI: 1.27–3.07). In addition, PCB-52 was positively associated with all blood glucose values of the oral glucose test ($p < 0.05$).

Marushka et al. (2017) investigate the potential associations between self-reported T2D and consumption of locally harvested fish, dietary long-chain omega-3 fatty acids (n-3FAs) and persistent organic pollutants intake among adult First Nations living on reserve in Ontario Canada. A significant positive association between fish consumption of one portion per week and more and T2D compared to no fish consumption was found (OR=2.5 (95% CI: 1.38–4.58). Dietary PCB intake was positively associated with T2D OR=1.07 (95%CI: 1.004–1.27) per unit increase in PCBs while n-3-FAs intake, adjusted for DDE/PCBs intake, showed an inverse or beneficial effect against T2D among older individuals (OR=0.86 (95% CI: 0.46–0.99). Mean PCB levels in fish ranged from 3.31 to 77.2 ng/g of fish (parts per billion; ppb). Marushka et al. (2018) investigated the association between fish consumption and the prevalence of type 2 diabetes in First Nations living on reserve in Manitoba and Ontario, Canada. PCB in Manitoba first nation fish ranging from 0.03 to 9.24 ng/g (ppb), while in Ontario first nation , PCB levels in fish range from 9 to 64 ng/g (ppb). PCB and DDE exposure was positively associated with type 2 diabetes in a dose-response manner. Stronger positive associations were found among females (OR = 14.96 (3.72–60.11)) than in males (OR = 2.85 (1.14–8.04)). The threshold of daily dietary PCB exposure that increase the risk of type 2 diabetes was 1.47 ng/kg/day. Each further 1 ng/kg/day increase in PCB intake increased the risk of type 2 diabetes with an OR of 1.44 (1.09–1.89).

PCBs and p,p′-DDE were also associated with increased risk of diabetes and higher fasting glucose level in a cross-sectional survey of Canadian Inuit (Singh and Chan 2017). Using multiple regression models adjusted for confounding factors (age, sex, BMI, HDL-C, omega-3/omega-6 ratio, and education), statistically significant positive ORs were found for PCBs 105, 118, 153, 156, 170, 180, 183, ΣPCB, and p,p′-DDE with lipid standardization (OR range: 2.2–3.5, lower 95% limit: 1.04–1.42, upper 95% limit: 4.67–8.95). These PCB congeners represent some of the most abundant, regularly detected congeners in populations with environmental PCB exposure and include dioxin-like congeners (105, 118, 156) and non-dioxin like congeners (153, 170, 180, 183). The highest vs. lowest quartile exposure to most PCBs and p,p′-DDE were associated with an increase of fasting glucose by 3–7%.

Grandjean et al. (2011) conducted a clinical examinations of 713 Faroese residents aged 70–74 years included fasting plasma concentrations of PCBs, glucose and insulin, and glycosylated hemoglobin (hemoglobin A1C). In nondiabetic subjects, the fasting insulin concentration decreased by 7% (95% CI -12% to -2%) for each doubling of the PCB concentration after adjustment for sex and body mass index at age 20. Conversely, the fasting glucose concentration increased by 6% (-1% to 13%) for each doubling in PCB. Impaired insulin secretion appears to constitute an important part of the type 2 diabetes pathogenesis associated with exposure to PCBs.

Gasull et al. (2012) assessed the relationship between POP serum concentrations and type 2 diabetes and prediabetes (impaired fasting glycemia; fasting plasma glucose between 110 and 125 mg/dL) in the general adult population of 886 residents of Catalonia (Spain). In models adjusted by age, sex, BMI, total cholesterol and triglycerides the prevalence of diabetes and prediabetes increased in a dose-dependent manner across quartiles of total PCBs, non-dioxin-like PCBs (PCBs 52, 101, 138, 153, 180), PCBs 118, 138, 153, and 180. It is important to note that only part of the association was due to age, sex, and BMI since in models adjusted by these three factors, the prevalence of diabetes and prediabetes continued to increase in a dose-dependent manner across quartiles of the PCBs, with odds ratios of diabetes between 2.3 and 3.2 for the upper quartile of PCBs. Concentrations of p,p′-DDT (dichlorodiphenyltrichloroethane), p,p′-DDE (dichlorodiphenyldichloroethene) and β-HCH (hexachlorocyclohexane) were not associated with diabetes or prediabetes. The results of this study support the conclusion that exposure to PCBs may be a diabetogenic factor in both obese and nonobese individuals. The associations found with PCB levels and prediabetes are also suggestive of a causal relationship with diabetes.

Using a prospective design, Wolf et al. (2019) conducted a nested case-control study examining PCB levels at baseline and the incidence of type 2 diabetes among participants of two population-based German cohort studies. The study utilized multivariable conditional logistic regression analysis adjusted for cohort, body mass index, total cholesterol levels, alcohol consumption, smoking status, physical activity, and parental diabetes. The authors observed an increased chance for incident diabetes for PCB-138 and PCB-153 with an odds ratio (OR) of 1.50 (95%CI: 1.07–2.11) and 1.53 (1.15–2.04) per interquartile range increase in the respective PCB congener. In addition, the sum of PCBs 138, 153 and 180 was also significantly associated with T2D with an OR of 1.29 (95% CI: 1.01 – 1.64), further supporting a positive association between PCB exposure and development of type 2 diabetes. No significant associations with T2D were found under these conditions for HCB (hexachlorobenzene), β-HCH (beta-hexachlorocyclohexane) or 4,4′-DDE (4,4′-dichlorodiphenyldichloroethylene). The main strengths of this study include the prospective study design, the use of incident diabetes cases and the selection of cases and controls from population-based cohort studies permitting generalizability of the results to the general population.

While most studies have reported that PCBs increase the risk of diabetes, two studies from Northern Italy did not observe this association. Raffetti et al. (2018) found that PCB exposure was related with subsequent development of hypertension and possibly cardiovascular diseases, but no association was found for diabetes and thyroid disorders. Zani et al. (2019) evaluated PCB serum levels and their associations with endocrine and metabolic diseases and hypertension in a random sample of 816 adults aged 20–79 years from Northern Italy. The study found that PCBs were not associated with thyroid diseases, diabetes and hypertension or with hormone serum levels and glycemia when taking account of age, gender, education, smoking habits and BMI in the general population living in a highly PCB polluted area. However, the authors indicated that medium- and high-chlorinated PCBs contributed most to the total PCBs, whereas dioxin-like PCBs and low chlorinated PCBs, which were the only PCB congeners associated with diabetes and hypertension in some studies, contributed less than 5% to the sum of total PCBs. The authors also stated that the cross-sectional study design and the collection of subjects' self-reported data on the presence of chronic diseases may be of concern.

The potential mechanism(s) for the association between elevated serum PCBs and the metabolic syndrome, insulin sensitivity and insulin secretion was reviewed by Everett et al. (2011). In animal and human cell studies, various PCBs appear to alter glucose and insulin metabolism. These studies specifically show effects on the glucose transporter (GLUT-4) gene and protein; insulin-like growth factor binding protein-1 (IGFBP-1); nuclear transcription factor kappa B (NFkB); tumor necrosis factor alpha (TNFα); and insulin production. Baker et al. 2013, reported further mechanistic data showing that coplanar PCBs impaired glucose homeostasis in lean mice and in obese mice following weight loss. They also found that adipose-specific elevations in TNF-α expression by PCBs may contribute to impaired glucose homeostasis.

Thus, it is clear from consistent epidemiological and mechanistic studies and review articles, including meta-analysis, that PCBs are a risk factor for type 2 diabetes and with increasing exposure, there is an increase in the risk of developing this disease.

b. Thyroid Dysfunction

PCBs interfere with the production, transportation and metabolism of thyroid hormones, in addition to having the ability to bind to thyroid receptors and modulate thyroid hormone signaling. PCBs have adverse effects on the thyroid, due in part to the ability of PCBs and their metabolites to bind to thyroid transport proteins, such as transthyretin (TTR), displacing thyroxine (T4) and disrupting thyroid function. PCB metabolites, such as PCB sulfates can also alter serum thyroid hormone levels in humans by binding to TTR. The ability of PCBs to interfere with thyroid function contributes to the neurodevelopmental abnormalities in the fetus and young children and has been associated with thyroid abnormalities in adults (reviewed by Duntas and Stathatos, 2016).

Julvez et al. (2011) assessed thyroid dysfunction as a mediator of organochlorine (PCB and *p,p'*-DDE) neurotoxicity in preschool children. It has been proposed that OC developmental neurotoxicity may result in part from OC-mediated impairment of thyroid function during the critical period of intense neurodevelopment (Chevrier et al. 2008), in addition to other mechanisms, for example, involving oxidative stress (Morales et al. 2008). Resin triiodothyronine uptake ratio (T3RU) was assessed as an estimate of the amount of thyroxine-binding globulin (TBG) sites unsaturated by thyroxine. The investigators found consistent inverse associations between maternal serum and breast milk PCB levels and cord blood T3RU after covariate adjustments. The results suggest that PCB exposures may decrease the T3RU during pregnancy and at birth. In addition, minor decreases of the thyroid function may be inversely associated with a child's neurodevelopment. Adjusted regression models suggested that decreased thyroid function may be associated with neurobehavioral deficits that are similar to those related to OC exposures, and PCBs in particular. The validity of this study is supported by the thyroid and OC assessments being based on multiple sets of samples, such as maternal serum (both parameters), cord serum (thyroid measures), and breast milk (OC concentrations).

Many epidemiologic studies among adults exposed to PCBs have reported lower levels of total T_4 in relation to exposure, although the literature is somewhat inconsistent overall (Salay and Garabrant 2009). In Michigan adults, PCB congeners 118, 138, 153, and 180 were statistically significantly associated with greater total and free thyroxine and total triiodothyronine among women and with total and free triiodothyronine among men (Jacobson et al., 2017). Another study

of 2,046 adults from a polluted area in eastern Slovakia found negative associations between serum PCBs and total T_3 and free T_4 at lower PCB exposure levels (<530 ng/g lipid), but positive associations were observed at greater exposure levels (Langer et al. 2007a). In a related study, Langer et al. (2007b) found that thyroid volume in groups of males and females with high PCBs level was significantly higher than in age and sex matched groups with low PCBs level. Together, the results suggest that the thyroid is a target for the toxicity of PCBs, but the findings in adults may vary from that in younger populations.

PCBs are generally believed to be endocrine-disrupting chemicals (EDCs) in humans and animals. Eskenazi et al. (2017) examined the relationship of in utero and childhood exposure to PCBs and reproductive hormones in adolescent boys who participated in CHAMACOS, an ongoing birth cohort in California's Salinas Valley. PCBs were measured in serum collected from mothers during pregnancy or at delivery and from their sons at 9 years. A 10-fold increase in total prenatal PCBs was associated with a 64.5% increase (95% CI: 8.6, 149.0) in follicle-stimulating hormone (FSH) in the male offspring, primarily driven by non- dioxin-like congeners.

Miyashita et al. (2018) reported sex-related differences in the associations between maternal dioxin-like PCBs and reproductive and steroid hormones in cord blood in the Hokkaido study. An increase in the levels of maternal non-ortho PCBs was also significantly associated with a decrease in the testosterone/ estradiol (T/E2) ratio, a decrease in the sex hormone-binding globulin (SHBG), a decrease in inhibin B levels, an increase in androstenedione, dehydroepiandrosterone (DHEA) levels, an increase in adrenal androgen/glucocorticoid (AA/GC) ratio, and an increase in FSH in male cord blood samples. However, an increase in the levels of maternal monoortho PCBs was significantly associated with a decrease in DHEA levels as well as a decrease in AA/GC ratios in female cord blood samples. In contrast, an increase in the levels of maternal mono-ortho PCBs was significantly associated with an increase in cortisol, cortisone, and SHBG levels. Therefore, sex-related differences were observed in the relationships between maternal dioxin-like PCBs and cord blood hormones. These results suggest that in utero exposure to PCBs modifies steroidogenesis and suppresses the secretion of inhibin B.

Baba et al. (2018) investigated the effect PCBs during pregnancy on maternal and neonatal thyroid hormone levels (thyroid stimulating hormone (TSH) and free thyroxine (FT4)) in a prospective birth cohort consisting of 386 mothers and 410 infants. Multiple linear regression analysis found coplanar PCBs positively associated with neonatal FT4 at 4-7 days of age (beta=0.206), with boys having a stronger association (beta= 0.282). Nine out of thirteen DL-PCBs (#81, 105, 118, 123, 126, 146, 157, 167, 169) and three out of 58 NDL-PCBs (#37, 202, 206) were significantly associated with elevated neonatal FT4. No groupings or congeners had a significant association with neonatal TSH. Non-ortho PCBs were positively associated with maternal FT4 at early gestational stage (median 10 weeks) and three PCB congeners had significant positive association(s) with maternal THs (#47 and #52with TSH, #77 with FT4, #52 with TSH × FT4). The study concludes that perinatal exposure to background-level DLCs increases neonatal FT4, especially in boys.

8. Immune System Dysfunction in Humans Exposed to PCBs

Park et al. (2008) examined the effects of prenatal exposure to PCBs on thymus size at birth in Eastern Slovakian neonates. Prenatal PCB exposure was associated with a smaller thymic index at birth. This evidence suggests that PCB exposure in neonates is associated with a smaller thymic volume, leading to the possibility of impaired immunologic development.

Dallaire et al. (2006) evaluated the associations between PCB-153 concentration in umbilical cord plasma and the incidence rates of acute otitis media (AOM) and of upper and lower respiratory tract infections (URTIs and LRTIs, respectively) in Inuit children 0 to 5 years of age. The incidence rates of AOM and LRTIs were positively associated with prenatal exposure to PCBs. Compared with children in the first quartile of exposure (least exposed), children in fourth quartile (most exposed) had rate ratios of 1.25 ($p < 0.001$) and 1.40 ($p < 0.001$) for AOM and LRTIs, respectively. There was no association between prenatal PCB exposure and incidence rate of URTIs or hospitalization. Two earlier studies in this Inuit population also found the relationship between prenatal PCB exposure and increase incidence of acute infection in infants (Dewailly et al., 2000; Dallaire et al., 2004). The Norwegian Mother and Child Cohort Study found maternal dietary exposure to PCBs to be associated with an increased risk of wheeze and more frequent upper respiratory tract infections in children during the first 3 years of life (Stolevik et al., 2013). Maternal exposure to dietary PCBs was also found to be associated with reduced antibody response to a measles vaccine in children at 3 years of age. Together, the results of these studies support the negative impact of PCBs on the developing immune system

Heilmann et al. (2006) also found that PCB exposure was a possible cause of deficient immune function in children. They demonstrated that increased perinatal exposure to PCBs can adversely affect immune responses to childhood vaccinations. The study examined sera for antibody responses against diphtheria and tetanus vaccines from 119 children at 18 months and 129 children at 7 years of age. The antibody response to diphtheria vaccine decreased at age 18 months by 24.4% (95% CI = 1.63-41.9; $p = 0.04$) for each doubling of the PCB exposure at the time of examination. At age 7 years, antibody response to tetanus vaccine decreased by 16.5%. In a subsequent study, Heilmann et al 2010 assessed the dependence of antibody concentrations against diphtheria and tetanus toxoids in children with regard to prenatal and postnatal PCB exposures. At age 5 years, before the booster vaccination, the antidiphtheria antibody concentration in 587 Faroe Islands children was inversely associated with PCB concentrations in milk and 18-month serum. Results obtained 2 years later showed an inverse association of concentrations of antibodies against both toxoids with PCB concentrations at 18 months of age. The strongest associations suggested a decrease in the antibody concentration by about 20% for each doubling in PCB exposure. At age 5 years, the odds of an antidiphtheria antibody concentration below a clinically protective level of 0.1 IU/L increased by about 30% for a doubling in PCB in milk and 18-month serum. The results indicate that developmental PCB exposure is associated with immunotoxic effects on serum concentrations of specific antibodies against diphtheria and tetanus vaccinations. Because of the involvement of several key components of the immune system (antigen presentation, T-lymphocyte function, and B-lymphocyte function), antibody concentrations triggered by standardized antigen stimulations may reflect the overall function of the immune system in relation to infection.

The impact of early-life exposure to PCBs on response to infant tuberculosis vaccination was assessed in families participating in a prospective birth cohort in eastern Slovakia (Jusko et

al., 2016). At 6 months, infants are given BCG, a live, attenuated vaccine generally administered around the time of birth to reduce severe forms of tuberculosis in early childhood. Higher 6-month infant concentrations of PCB-153 were associated with lower 6-month BCG-specific antibody levels. BCG-specific IgG levels were 37% lower for infants with PCB-153 concentrations at the 75th percentile compared to the 25th percentile (95% CI: –42, –32; $p < 0.001$). The study demonstrated that PCB exposures contributed to poorer responses to BCG vaccine, however the association between these exposures and tuberculosis incidence is unknown.

Haase et al. (2016) examined the relationship between PCB body burden and indicators of immune function was investigated as part of the HELPcB (Health Effects in High-Level Exposure to PCB) program, offering bio-monitoring to workers, relatives, and neighbors exposed to PCBs by a German transformers and capacitors recycling company. Immediately after the end of exposure, the findings include a significant positive correlation between congeners with low to medium chlorination and the relative proportion of CD19 positive B-cells among lymphocytes, a negative correlation of PCB114 with serum IgM, and of PCB 28 with suppressor T-cell and NK-cell numbers. Congeners with a high degree of chlorination were positively associated with expression of the activation marker CD25 on T-cells in the cohort at one year after the end of exposure. Thus, PCBs alter the cellular composition of adaptive immunity, affecting both T- and B-cells, however, the values were not generally outside the reference ranges for healthy adult individuals. While not indicating overt functional immunodeficiency, the results indicate that PCBs modify immune parameter.

9. Cardiovascular Disease in Human Exposed to PCBs

Epidemiological evidence now implicates exposure to PCBs with an increased risk of developing diabetes, hypertension, lipid abnormalities and obesity, all of which are clinically relevant to the onset and progression of cardiovascular disease (reviewed by Perkins et al., 2016). PCBs may modulate cellular signaling pathways leading to induction of chronic oxidative stress, inflammation, and endocrine disruption that contribute to a range of adverse health outcomes. Recent mechanistic studies by Wang et al. (2019) found that PCB 126 can contribute to macrophage polarization and inflammation, through both AhR and NF-κB signaling pathways, indicating another possible role of dioxin-like PCBs in the pathology of atherosclerosis. These findings have translational implications, suggesting that environmental insults from dioxin-like PCBs can contribute to chronic diseases by modulating inflammatory cascades within immune cells creating an advantageous environment for cardiovascular disease progression.

Goncharov et al. (2010) found associations between total PCB concentrations (sum of 35 congeners) and systolic blood pressure, and diastolic blood pressure among residents of Anniston, AL that were not on hypertension medication. Everett et al. 2008a studied participants in the NHANES 1999–2002. The association of 11 PCB congeners with hypertension (diagnosed and undiagnosed [≥140/90 mmHg]) was assessed in age, gender, race, smoking status, body mass index, exercise, total cholesterol, and family history of coronary heart disease adjusted logistic regressions. Both dioxin-like PCBs congeners 74, 118, 126, 156, and 169, and non-dioxin-like PCBs 99, 138/158, 153, 170, 180, and 187 were evaluated. The congeners found to be associated with hypertension were PCBs 126, 74, 118, 99, 138/158, 170, and 187. Everett et al. 2008b also studied participants in the NHANES 1999–2004. The associations of the same 11 PCB congeners with hypertension were evaluated again using 2 years additional data. Dioxin-like PCB congeners

74, 118, and 126 were significantly related to hypertension in the expanded analysis. In a related study in Anniston AL, Aminov et al. (2013) found that increased total serum PCB concentrations was significantly associated with elevated concentrations of total cholesterol and triglycerides, but found no effect on HDL or LDL cholesterol. Thus, in addition to hypertension, there is a clear association between PCBs and elevation in serum lipids, a major risk factor for cardiovascular disease.

Valera et al (2013) found a significant association between PCB 105, PCB 118 and the sum of dioxin-like PCBs (sum of 105, 118, 156) and hypertension in 18-39 year old Inuit from Greenland when the analysis was adjusted for age, sex, BMI, diabetes, physical activity and smoking. In this age group, the sum of non-dioxin like PCBs had an elevated adjusted OR of 1.27 but was just under that needed to reach statistical significance (0.96 – 1.69, 95% CI).

Donat-Vargas (2018) assessed the association with blood pressure levels and hypertension in a longitudinal study over 10 years with repeated measurements in a sample of middle-aged men and women. Association for DL-PCBs remained statistically significant after lipid-standardization and adjustment for body mass index and total serum lipids. The multivariable-adjusted odds ratio of hypertension based on repeated measurements were 1.52 (95% confidence interval, 1.08–2.13) for DL-PCBs 118 and 156. In stratified adjusted analyses, odds ratio for those born after 1950 increased to 3.99 (95% confidence interval, 2.15–7.43), whereas no association was observed among those born earlier. Strengths of the study are a large sample size (n=850), with adequate statistical power, and a longitudinal design with repeated measurements during the 10-year follow-up. By prospectively examining the association of early POP levels and development of hypertension it is possible to avoid reverse causation bias and take into account long-term POP exposure. Based on repeated measurements, the accumulated exposure to DL-PCBs may disrupt the normal blood pressure levels and increase the odds of hypertension.

Rafetti et al. (2018) conducted a study in Brescia (North Italy) in a cohort of 1331 subjects with at least one measure of PCB serum levels, during the period from 2001 – 2013, and followed the participants longitudinally for the incidence of hypertension, cardiovascular diseases, and endocrine and metabolic chronic diseases (from Brescia Health Protection Agency database). Poisson regression models adjusted for age, level of education, BMI, cholesterol level, tobacco smoking and alcohol drinking were used to calculate rate ratios (RRs). A dose-response relationship was observed between PCB serum levels and the onset of hypertension (RR for 2nd and 3rd tertiles of serum PCB distribution: 2.07, 95% CI 1.18–3.63, and 2.41, 1.30–4.47, respectively). While the study found that PCB exposure was related with subsequent development of hypertension and possibly cardiovascular diseases, no association was found for diabetes and thyroid disorders.

Singh and Chan (2018) investigated the association of serum PCBs with high cholesterol and related parameters which are known risk factors for cardiovascular disease in Canadian Inuit. PCBs were associated with increased risk of high cholesterol and higher levels of serum triglycerides, total cholesterol, and LDL-C, all of which are risk factors for heart disease. No association was observed between PCBs and serum HDL-C, also referred to as "good cholesterol" which reduces the risk of heart disease.

Recently, a prospective study in an elderly Swedish cohort assessed the association of serum PCBs, measured at ages of 70 and 75 years, with risk of mortality over a 10 year period, tracked from age 70 to 80 years (Lind et al., 2019). Elevated levels of highly chlorinated PCBs were associated with increased mortality risk, especially from cardiovascular diseases (CVD). This is despite the fact that there were fewer deaths due to CVD relative to all other causes. The sum of the highly chlorinated PCBs (PCBs 209, 206, 194, 189, 180, 170, 157, and 156) was significantly associated with all-cause mortality, while the sum of the less chlorinated PCBs (PCBs 153, 138, 118, 105, 99, and 74) was not significantly associated with all-cause mortality. Following adjustment for hypertension, diabetes, smoking, body mass index, education, and CVD at baseline, PCBs 206, 189, 170, and 209 were still associated with all-cause mortality (PCB 206: adjusted hazard ratio (HR) 1.47, 95%CI, 1.19-1.81; PCB 189: adjusted HR 1.29, 95%CI, 1.08-1.55; PCB 170: adjusted HR 1.24, 95%CI, 1.02-1.52; PCB 209: adjusted HR 1.29, 95%CI, 1.04-1.60), while the elevated HR for other PCBs did not reach the level of statistical significance. The repeated measurements of PCB levels from the same individuals at 2 occasions gave a more accurate estimation of PCB levels and increased the power of the statistical analysis compared with previously conducted studies. The association of elevated cardiovascular mortality with serum PCBs is supported by a previous cross-sectional study which found a positive association between serum concentrations of PCBs and the prevalence of CVD in NHANES, which represents a sample of the U.S. population (Ha et al., 2007). In a separate analysis of NHANES data, Fry et al., 2017 found no association between PCBs and mortality. Importantly, this NHANES-based study and other studies did not measure the most highly chlorinated PCBs (PCBs 206, 194, 209, and 189) and it was among those highly chlorinated PCBs that the most powerful associations with mortality were found in the study by Lind (2019). Importantly, the conclusion of Lind (2019) that elevated levels of highly chlorinated PCBs were associated with increased mortality risk, especially from cardiovascular diseases (CVD), is supported by epidemiological evidence implicating exposure to PCBs with an increased risk of developing diabetes, hypertension, lipid abnormalities and obesity, all of which are clinically relevant to the onset and progression of cardiovascular disease (reviewed by Perkins et al., 2016).

Lim et al. (2018) recently utilized large prospective cohort data from the Korean Cancer Prevention Study-II to conduct a case-cohort study to evaluate the association between serum PCB levels and type of stroke risk. They utilized the weighted Cox regression model, adjusting for potential confounding factors, including age, sex, body mass index, smoking status, physical activity, family history of cardiovascular disease, and hypertension. After adjusting for potential confounding factors, increased risk for stroke was observed among participants with serum concentration of PCB 118 (HR = 2.33, 95% CI:1.04, 5.22), PCB156 (HR = 3.42, 95% CI: 1.42, 8.23), and PCB138 (HR = 3.80, 95% CI: 1.48, 9.76). PCBs were positively associated with ischemic stroke, but not with hemorrhagic stroke.

Donat-Vargas et al. (2015) prospectively assessed the association between dietary intake of PCBs and the incidence of hypertension in a Spanish cohort of 14,521 university graduates, free of hypertension at baseline and followed-up for a median of 8.3 years. Dietary intake of PCBs was assessed at baseline through a previously validated food frequency questionnaire. During follow-up, 1497 incident cases of medically diagnosed hypertension were identified. After adjusting for potential confounders (age, sex, smoking, physical activity, total energy intake, fast-food consumption, sitting hours, sugar soft drinks consumption, following special diet, hypercholesterolemia, family history of hypertension, fried food consumption, alcohol

consumption, use of aspirin and non-aspirin analgesics, caffeine intake, cereal fiber intake, low-fat dairy intake, olive oil intake, fruit and vegetables intake, energy-adjusted fatty fish consumption, and energy-adjusted sodium and potassium intake), participants in the fifth quintile of total PCBs intake were at higher risk of developing hypertension (adjusted hazard ratio, 1.43 [95% confidence interval, 1.09–1.88; *P* for trend 0.017]) compared with those in the first quintile.

In a series of related prospective, population-based studies, incident cases of myocardial infarction, heart failure, and stroke were found to be significantly associate with increased dietary exposure to PCBs (Bergkvist et al., 2014, 2015, 2016; Akersson et al., 2019). The association between dietary exposure to PCBs and the risk of cardiovascular disease were assessed in two large population based prospective cohorts of Swedish women and men, taking into account the beneficial effect of long-chain omega-3 fish fatty acids from fish. The studies used validated estimates of dietary PCBs (Bergkvist et al., 2012) and long-chain omega-3 fish fatty acids obtained from a food frequency questionnaire at baseline (1997). PCBs are mainly found in food of animal origin and in particular fatty fish from contaminated waters can contain high levels of PCBs. The major dietary sources of PCB exposure are fish (67%), dairy products (19%) and meat products (9%). Incident cases of cardiovascular disease over 12 years following baseline (1997) were obtained through the Swedish National Patient Register and the Swedish Cause of Death Register.

Bergkvist et al. (2014) assessed the association between dietary PCB exposure and stroke risk with the intake of long-chain omega-3 fish fatty acids. The prospective population-based Swedish Mammography Cohort was comprised of 34,591 women free of cardiovascular diseases and cancer at baseline in 1997 and followed up for 12 years. Validated estimates of dietary PCB exposure were obtained via a food frequency questionnaire at baseline and incident cases of stroke were obtained through register linkage. During 12 years of follow-up, there were 2015 incident cases of total stroke (1532 ischemic strokes, 216 intracerebral hemorrhages, 94 subarachnoid hemorrhages and 173 unspecified strokes). Multivariable adjusted relative risks (RR) were controlled for known stroke risk factors, age, education, family history of myocardial infarction before the age of 60 years, high cholesterol, history of hypertension, atrial fibrillation before baseline, ever use of postmenopausal hormones, use of aspirin, smoking status, body mass index, parity, use of fish oil supplements, alcohol consumption, total physical activity, energy intake, consumption of fruit and vegetables, red and processed meat and dairy products, dietary MeHg exposure and high-, medium- and low-fat fish consumption. Dietary PCBs were significantly associated with total stroke (RR 1.67, 95% confidence interval (CI), 1.29–2.17), ischemic stroke (RR 1.61, 95% CI, 1.19–2.17) and hemorrhagic stroke (RR 2.80, 95% CI, 1.42–5.55) for women in the highest quartile of dietary PCB exposure (median 288 ng /day) compared with women in the lowest quartile (median 101 ng /day). In addition, omega-3 fish fatty acids or fish intake was associated with a protection from stroke risk after adjusting the models for dietary PCB exposure.

Bergkvist et al. (2015) assessed the association between dietary PCB exposure and myocardial infarction risk with the intake of long-chain omega-3 fish fatty acids. The prospective population-based Swedish Mammography Cohort was comprised of 33,446 women free from cardiovascular disease, cancer and diabetes at baseline (1997) and followed up for 12 years. Validated estimates of dietary PCB exposure were obtained via a food frequency questionnaire at baseline and incident cases of myocardial infarction were obtained through register linkage. During 12 years of follow-up, there were 1386 incident cases of myocardial infarction. Women in the highest quartile of dietary PCB exposure (median 286 ng/day) had a significantly increased

risk of myocardial infarction, with a multivariable-adjusted relative risk (RR) of myocardial infarction of 1.21 (95% CI, 1.01–1.45) compared to the lowest quartile (median 101 ng/day). Notably, the RR increased to 1.58 (95% CI, 1.10–2.25) after adjusting for the protective effect of long-chain omega-3 fish fatty acids.

In a related study conducted in the same cohort, Bergkvist et al. (2016) assessed the association between dietary PCB exposure and risk of myocardial infarction among 36,759 men from the population-based Swedish Cohort of Men, free of cardiovascular disease, diabetes and cancer at baseline in 1997. During 12 years of follow-up, 3005 incident cases of myocardial infarction (654 fatal) were identified. Compared with the lowest quintile of dietary PCB exposure (median 113 ng/day), men in the highest quintile (median 436 ng/day) had multivariable-adjusted relative risks of 1.74 (95% confidence interval [CI], 1.30–2.33; p trend < 0.001) for total and 1.97 (95% CI 1.42–2.75; p-trend < 0.001) for non-fatal myocardial infarction. Multivariable-adjusted relative risks were adjusted for age, education level, family history of myocardial infarction before the age of 60 years, high cholesterol, hypertension, use of aspirin, smoking status, waist circumference, total physical activity, use of fish oil supplements, alcohol consumption, energy intake, consumption of fruit and vegetables, dairy products and consumption of red and processed meat, dietary intake of saturated fatty acids, dietary MeHg exposure, and dietary intake of omega-3 fatty acids. The study also found an effect modification by adiposity on the association between dietary PCB exposure and myocardial infarction, with higher risk among lean men (p value for interaction =0.03).

Akesson et al. (2019) assess the association between dietary exposure to PCBs and the risk of heart failure in two large population based prospective cohorts of Swedish women and men, taking into account the beneficial effect of long-chain omega-3 fish fatty acids from fish. The large study consisted of 32,952 women and 36,546 men, free from cancer, cardiovascular disease and diabetes at baseline in 1997. Validated estimates of dietary PCBs (Bergkvist et al., 2012) and long-chain omega-3 fish fatty acids were obtained from a food frequency questionnaire at baseline and incident cases of heart failure were obtained through the Swedish National Patient Register and the Swedish Cause of Death Register. The dietary PCB exposure was based on the concentration of the PCB congener 153, which is the most commonly occurring congener in food on the Swedish market and, thus, a good indicator of both total PCBs and the dioxin-like PCBs in food as well as human blood. During an average of 12 years of follow-up, there were 2736 and 3128 incident cases of heart failure in women and men, respectively. In multivariable-adjusted models, mutually adjusted for PCBs and omega-3 fatty acids, the relative risk (RR) for dietary PCB exposure was 1.48 (95% CI 1.12–1.96) in women and 1.42 (95% CI 1.08–1.86) in men, comparing extreme quintiles. Corresponding RRs for omega-3 fish fatty acids intake were 0.71 (95% CI 0.54–0.93) and 0.82 (95% CI 0.63–1.07), in women and men, respectively. Multivariable-adjusted relative risks were adjusted for attained age, education, waist circumference, weight loss, leisure-time inactivity and daily walking/cycling, family history of myocardial infarction before the age of 60 years, high cholesterol, history of hypertension, smoking status and pack-years of smoking, use of aspirin, energy intake, Mediterranean diet score and methylmercury and dietary PCB or omega-3 fish fatty acids intake. The important conclusions from the study are that dietary exposure to PCBs was associated with an increased risk of heart failure in both women and men, while omega-3 fish fatty acids intake was associated with a lower risk of heart failure.

Together, the above studies indicate that background levels of exposure to PCBs are associate with elevated risk of hypertension and cardiovascular disease, including myocardial infarction, heart failure, and stroke. In addition, dietary studies suggest that PCB may counteract the beneficial effect of long-chain omega-3 fish fatty acids on cardiovascular disease (Bergkvist et al., 2014, 2015, 2016; Akersson et al., 2019). Furthermore, to promote fish consumption as a healthy food alternative in cardiovascular guidelines the levels of PCBs in fish should be reduced as much as possible.

10. Metabolic Syndrome in Humans Exposed to PCBs

Metabolic Syndrome is a cluster of cardiovascular disease risk factors which include central obesity, hypertension, dyslipidemia and dysglycemia. Individuals with metabolic syndrome have a greater risk of development of cardiovascular diseases and type 2 diabetes, which in turn are associated with increased morbidity and mortality. PCBs have previously been linked to the metabolic syndrome and its components in cross-sectional studies (Lee et al., 2007; Lind et al., 2013). In the Anniston Community Health Survey, summed PCB concentrations were significantly and positively associated with metabolic syndrome only in unadjusted models; adjustment resulted in attenuation of the ORs in both the quintile and log transformed models (Rosenbaum et al., 2017).

In a cross-sectional study of morbidly obese persons (body mass index, BMI >35 kg/m^2 and comorbidity or BMI >40 kg/m^2), the odds of metabolic syndrome were increased with higher concentrations of dioxin-like and non-dioxin-like PCBs (Dusanov et al., 2018). Subjects with type 2 diabetes were excluded as the focus of the present study was on cardiometabolic risks. Age-adjusted concentrations of dioxin-like and non-dioxin-like polychlorinated biphenyls (PCBs) increased with number of metabolic syndrome components (large waist circumference, hypertension, elevated triglycerides, low HDL-cholesterol, and elevated fasting glucose) in both genders ($p < 0.001$). Dioxin-like PCBs were associated with metabolic syndrome, diastolic blood pressure and fasting glucose, as well as with HOMA-IR index. Non-dioxin-like PCBs were associated with metabolic syndrome and fasting glucose, large waist circumference, hypertension, elevated triglycerides, low HDL-cholesterol, and elevated fasting glucose.

Gasull et al. (2018) recently investigated the relationships between serum concentrations of PCBs and metabolic phenotypes in 860 normal-weight, overweight, and obese participants in the general adult population of Catalan, Spain. In models adjusting for age, sex, body mass index, cigarette smoking, alcohol consumption, physical activity, and occupational social class, PCBs were associated with the unhealthy metabolic phenotype (defined as 2 or more of the following: abdominal obesity, hypertriglyceridemia, low HDL cholesterol, hypertension, hyperglycemia) and metabolic syndrome (defined as 3 or more of the following: abdominal obesity, hypertriglyceridemia, low HDL cholesterol, hypertension, hyperglycemia).

PCB concentrations are associated with unhealthy metabolic phenotypes in obese and overweight individuals as well as and in normal-weight individuals. In a smaller study conducted in Spain, no statistically significant association was found between PCB levels in adipose tissue and metabolic syndrome (Mustieles et al., 2017).

In a prospective study, Lind et al. (2017) measured blood PCB levels at baseline in 452 subjects without metabolic syndrome from the Prospective Study of the Vasculature in Uppsala Seniors (PIVUS) study (50% women, all aged 70 years) and during 10-year follow-up, 92 incident cases of the metabolic syndrome occurred. PCB126 and PCB118, showed positive associations with future development of the metabolic syndrome independently of each other and in an additive fashion in this prospective study.

Based on the consistency of published studies, PCBs should be considered a risk factor contributing to the development of metabolic syndrome.

11. Cancer in Humans Exposed to PCBs

Due to the exceptional persistence of PCBs in the body, excess environmental exposure to these compounds over many years results in a long term, life-long increase in cancer risk, due to the potent long-term initiating and tumor promoting activity of PCBs in the body. Carcinogenicity of PCBs in humans has been investigated in retrospective occupational cohort studies that evaluated cancer mortality in workers and in case-control studies of the general population that examined associations between cancer and serum or adipose tissue levels of PCBs resulting from general background environmental exposures. PCBs have been associated with a statistically significant increased risk of cancer at several sites, including, but not limited to, the liver, biliary tract, gastrointestinal tract, pancreas, lung, non-Hodgkin's lymphoma (NHL), and skin (melanoma) in human studies and provide evidence that PCBs are carcinogenic [case-control studies at general background levels of PCBs: (NHL, Rothman et al. 1997; Hardell et al. 1996; Nordstrom et al. 2000; De Roos et al., 2005), (Pancreatic cancer, Hoppin et al. 2000; Porta et al.1999), (colorectal cancer, Howsam et al., 2004)]; [cancer mortality in occupational PCB studies: Brown 1987; Brown and Jones 1981; Nicholson and Landrigan 1994; Gustavsson et al. 1986; Gustavsson and Hogstedt 1997; Bertazzi et al. 1987; Kimbrough et al. 1999; Prince et al., 2006; Sinks et al., 1992].

The IARC Working Group performed a comprehensive review of the overall evidence for carcinogenicity of PCBs, on the basis of human carcinogenicity data, animal carcinogenicity and mechanistic data (IARC, 2016; Lauby-Secretan et al., 2016). The Working Group concluded that there was sufficient evidence for carcinogenicity of PCBs in humans for malignant melanoma and limited evidence for NHL and breast cancer (Lauby-Secretan et al., 2013; IARC, 2016). PCBs have been identified as Group 1, known human carcinogens, by the International Agency for Research on Cancer (Lauby-Sectretan et al., 2013; IARC 2016). This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 12–19 February 2013. Regarding cancer in humans, IARC 2016 concluded that, "there is *sufficient evidence* in humans for the carcinogenicity of PCBs. PCBs cause malignant melanoma. Positive associations have been observed for non-Hodgkin lymphoma and cancer of the breast." The report states that dioxin-like PCBs (PCB-77, PCB-81, PCB-105, PCB-114, PCB-118, PCB-123, PCB-126, PCB-169, PCB-156, PCB-157, PCB-167, PCB-189) are carcinogenic to humans but also concluded that the carcinogenicity of PCBs cannot be solely attributed to the carcinogenicity of the dioxin-like PCBs. The rationale for the conclusion that PCBs are human carcinogens was stated as follows: "There is strong evidence to support a receptor-mediated mechanism for carcinogenesis associated with dioxin-like PCBs in humans, based upon demonstration of carcinogenicity in experimental animals and upon extensive proof of

activity identical to 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (TCDD) for every step of the mechanism described for TCDD-associated carcinogenesis in humans, including receptor binding, gene expression, protein-activity changes, cellular replication, oxidative stress, promotion in initiation–promotion studies and complete carcinogenesis in experimental animals."

IARC also used mechanistic data in the evaluation of the carcinogenicity of PCBs (Lauby-Secretan et al., 2016). The Working Group found that PCBs may exert their carcinogenicity via several mechanisms. "All PCBs may induce formation of reactive oxygen species, genotoxicity, immune suppression, an inflammatory response and endocrine effects, to various extents and through different pathways. The dioxin-like PCBs exert their effects primarily through AhR activation and the downstream cascade of related events—induction of the xenobiotic metabolizing enzymes, modulation of gene expression, DNA adduct formation through generation of reactive oxygen species, and binding to steroid and thyroid hormones, leading to endocrine disruption. Less chlorinated PCBs act more readily through metabolic activation, with formation of reactive electrophilic metabolites to drive their carcinogenicity." In addition, the Working Group "stressed that the carcinogenicity of PCBs as a whole cannot be attributed solely to the carcinogenicity of the dioxin-like PCBs."

The specific cancer with the strongest evidence in humans is malignant melanoma. However, there are other types of cancer, including non-Hodgkin lymphoma (NHL) and breast cancer, which have been associated with serum PCB levels (IARC 2016).

Excess risk for melanoma was reported in several studies, mainly cohort studies of workers in the manufacture of capacitors and transformers, and in electric power and equipment maintenance. A significant linear exposure–response trend was noted in the largest occupational study that found that PCBs increase mortality from malignant melanoma in electric utility workers exposed to PCBs (Loomis et al., 1997). Gallagher et al. (2011) conducted a case–control study of 80 cutaneous malignant melanoma (CMM) patients and 310 control subjects, assessing the impact of background, environmental plasma PCB levels on CMM, controlling for lifetime sun exposure information, along with data on pigmentation variables and sun sensitivity data. Strong associations were seen between risk of CMM and levels of non-dioxin-like PCBs (Adjusted OR = 7.02; 95% CI: 2.30–21.43 for highest quartile). The association of CMM with PCB exposure persisted after control for sun sensitivity and sun exposure, the major known environmental risk factor for this disease. The association of melanoma and PCBs was noted consistently in occupational studies in different industries in North America and Europe, and in studies of the general population with background environmental PCB exposures, with cohort and case-control designs. Thus, the Working Group concluded that there is sufficient evidence in humans for the carcinogenicity of PCBs.

a. Recent studies confirming elevated cancer mortality with occupational PCB exposures

Mortality among 7,061 PCB capacitor workers from New York was updated through 2008 by Kimbrough et al. 2015. Standardized mortality ratios (SMRs) for all cancers combined increased for females (SMR 114; 95 % CI 103–126), but did not differ from expected rates in males. Salaried male capacitor workers had a statistically significant increase in malignant

melanoma based on death certificate information. These finding were also reported by Ruder et al 2014, who studied a larger group of workers. Ruder et al. 2014 evaluates mortality among a cohort of 24,865 capacitor-manufacturing workers exposed to PCBs at plants in Indiana, Massachusetts, and New York and followed for mortality through 2008. Cumulative PCB exposure was estimated using plant-specific job-exposure matrices. External comparisons to US and state-specific populations used standardized mortality ratios, adjusted for gender, race, age and calendar year. Among long-term employees, melanoma mortality was elevated, while all-cause and all-cancer mortality were not elevated. In subgroups of long-term worker, increased mortality was observed in women for all cancers and intestinal cancer and elevated in men for melanoma. Standardized rates of stomach and uterine cancer and multiple myeloma mortality increased with estimated cumulative PCB exposure. Poisson regression modeling showed significant associations with estimated cumulative PCB exposure for prostate and stomach cancer mortality. Associations between estimated cumulative PCB exposure and stomach, uterine, prostate cancer and myeloma mortality confirmed previous positive findings (Prince et al., 2006b; Ruder et al., 2006).

Higher prostate cancer mortality has been observed at high cumulative PCB exposure in occupationally exposed electrical capacitor manufacturing workers (Ruder et al. 2014; Prince et al. 2006). Ruder et al (2017) evaluated cancer incidence in a cohort of PCB exposed workers. Incident cancers, identified using state registries, were compared to those in a national population using standardized incidence ratios (SIRs). They identified 3,371 invasive first primary cancer diagnoses among 21,317 eligible workers through 2007. Overall relative incidence was reduced. Significant elevations were observed for respiratory cancers overall (SIR 1.23, 95%CI 1.14– 1.33) and urinary organ cancers among females (SIR 1.27, 95%CI 1.01–1.53). Among men, prostate cancer incidence was reduced and not associated with cumulative PCB exposure although median exposures were significantly higher for aggressive compared to localized/regional prostate cancers. The authors concluded that previously observed associations with cumulative PCB exposure and prostate cancer mortality were not confirmed in this analysis of cancer incidence; however, prostate cancer stage may explain the apparent discrepancy. Men with aggressive prostate cancer had significantly higher levels of estimated cumulative PCB exposure than those with nonaggressive cancer.

Increased cancer mortality as of 2006 was also reported by Pesatori et al. (2013) in workers exposed to PCBs in two Italian capacitor manufacturing plants, including a significant increased mortality from biliary tract cancer among males (SMR 3.91; 95%CI 1.47-10.41), digestive cancer in the whole cohort (SMR 2.54; 95%CI 1.21-5.34), and brain cancer in Plant 1 (SMR 2.13; 95%CI 1.02-4.48). Stomach cancer showed an increasing risk with increasing duration of employment (p for trend=0.02). Mortality from lymphomas was increased in the whole cohort (12 deaths; SMR 1.89; 95%CI 1.07-3.32); 4 deaths from Hodgkin's disease (HD) were observed in Plant 1 yielding a higher than three-fold increased risk in women. A 65% increased mortality from non-Hodgkin lymphoma (NHL) was also observed in the whole cohort, and consistently across cohorts and genders.

In Mallin et al., (2004), the strongest association was seen for female liver/biliary cancer, particularly in those with 10 or more years of employment at a capacitor manufacturing plant and more than 20 years' latency. Females employed 10 or more years had a significantly elevated age, gender, and calendar year-adjusted standardized mortality ratios (SMRs) SMR of 6.2 for liver/biliary cancer. "The 4 females in this group all began working in 1944, and therefore would

have been exposed to chlorinated naphthalenes at least until 1952, when they were replaced by PCBs in all areas of the plant except small assembly. They also would have potential PCB exposure during the 5 or more years they worked after 1951." Previous studies of PCB-exposed workers have also found elevated liver cancer mortality in females (Brown et al. 1987, 1981); and males (Gustavsson and Hogstedt 1997).

b. Elevated risk of malignant melanoma with occupational and general background, environmental PCB exposures.

A medical surveillance program HELPcB (Health Effects in High-Level Exposure to PCB) was initiated in 2010 after human biomonitoring revealed increased blood levels of PCB in workers at a German capacitor and transformer recycling company, where PCB-contaminated material was not handled according to proper occupational hygiene. Elevated PCB levels were not only discovered in the workers, but due to contamination also in their relatives, as well as in workers of surrounding companies. Leijs et al., (2018) found a significant correlation between cutaneous hyperpigmentation and PCB/dioxin blood levels in 92 moderate-high exposed individuals. The probability of having hyperpigmentation on the skin was statistically significantly higher in workers with higher sum PCBs- (OR:1.09 (1.12–2.17)), dioxin-like (dl)-PCBs- (OR:1.56 (1.12–2.17)) and dioxin (PCDD/Fs) (OR:1.09 (1.02–1.16)) levels. In addition, they observed a higher incidence of acne and malignancies of the skin (malignant melanoma, basal cell carcinoma and mycosis fungoides) in the workers compared to (estimated) incidences of the normal population in Germany.

Donat-Vargas et al. (2017) assessed the association of validated estimates of dietary PCB exposure (Bergkvist et al., 2012) as well as the intake of long-chain n-3 polyunsaturated fatty acids, accounting for sun habits and skin type, with the risk of malignant melanoma in middle-aged and elderly women. The prospective population based study included 20,785 women at baseline in 2009 from the Swedish Mammography Cohort. There were 67 incident cases of melanoma during the 4.5 years of follow-up. After multivariable adjustments, exposure to dietary PCBs was associated with four-fold increased risk of malignant melanoma (hazard ratio [HR], 4.0 [95% CI, 1.2 to 13; P for trend 0.02]). After adjustment for dietary PCB exposure, long-chain n-3 polyunsaturated fatty acid intake mainly from fatty fish was protective and associated with 80% lower risk (HR, 0.2 [95% CI, 0.1–0.8; *P* for trend = 0.03]), comparing the highest exposure tertiles with the lowest. The results from this study suggest that dietary PCB exposure mainly from fatty fish is positively associated with an increased risk of melanoma at the levels to which the general population is exposed.

Cao et al. (2019) recently assessed the relationships between plasma levels of PCBs and cutaneous malignant melanoma (CMM) in a Chinese population, using a case-control study, including 450 CMM cases and 500 healthy controls. After adjusting for potential confounding factors, including family history of cancer, household income, cumulative lifetime Sun exposures, sun burns history, and sun burns in childhood, the plasma level of total PCBs remained significantly associated with CMM risk, with a 1.44-fold increased risk for those in the highest quartile compared to those in the lowest quartile (OR=1.44, 95% CI: 1.02–2.03, P for trend=0.031). Significantly increased ORs were also observed for individual PCB congeners (PCB52, PCB170 and PCB180). The results of this case-control study supports the hypothesis of a strong association between plasma levels of PCBs and CMM risk in a Chinese population. This conclusion is

consistent with most studies carried out in North America and Europe, which provided evidence for an association between PCB exposure and melanoma risk.

Magonia et al., (2018) examined the relationship between PCB plasma levels and risk of CMM adjusting for sun sensitivity and sun exposure in a province of Northern Italy (Brescia), where a chemical factory produced PCBs from 1938 to 1984 causing human contamination in the general population. No association between the risk of CMM and plasma levels of total PCBs or specific congeners was found in this case–control study of 205 CMM patients and 205 control subjects. Several factors may contribute to the lack of a significant association in this study, in contrast to the positive associations observed in the case-control study of Cao et al. (2019). In addition to differences in skin characteristic in Chinese participants, the Cao study had a larger study population, with 450 CCM cases and 500 healthy controls relative to the Magonia study with 205 CMM patients and 205 controls. Another important difference was that the PCB levels in cases and controls were greater in the Cao study relative to the Magonia study. Total PCBs in the 75^{th} percentile controls was 12.9 ng/ml in Cao et al. (2019) and 5.0 ng/ml in Magonia et al. (2018). Similarly, the levels of individual PCB congeners were also higher in Cao et al. (2019), who reported significantly increased odds ratios for CMM with PCBs 52, 170 and 180. A notable difference in PCB exposures in these two studies is highlighted by the fact that none of the participants in Magonia et al. (2018) had detectable levels of PCB 52, which was found in the majority of participants in the Cao et al. (2019) study, in addition to being significantly associated with CMM.

In summary, while the recent case-control studies of Cao et al. (2019) and Magonia et al. (2018) differ in their conclusions, the strengths of Cao et al. (2019), including larger study population and greater range of exposures to PCBs support the IARC conclusion that PCBs cause malignant melanoma.

Two recent meta-analyses assessed the risk of malignant melanoma with exposure to PCBs. Boffetta et al. (2018) concluded that the results of their analysis "lend no support to the hypothesis of an association between exposure to PCBs and the risk of melanoma from either industry-based or community-based studies, although the results of internal analyses of selected studies are supportive of an association." At approximately the same time, and from the same institution (Department of Medicine and Surgery Specialties, Radiological Sciences and Public Health, University of Brescia, Italy), Zani et al. (2017) re-evaluated the association between exposure to PCBs and risk of melanoma by a systematic review and meta-analysis. They reported a statistically significant increased risk for melanoma with PCB exposure (pooled standard mortality ratio (SMR) of 1.32; 95% CI: 1.05-1.64). However, Zani et al., 2017 attempt to dismiss this association as invalid, citing possible biases and inconsistencies among the studies and concludes that the findings "do not provide a strong evidence that PCB exposure can increase the risk of melanoma."

Both studies by Boffetta et al. (2018) and Zani et al. (2017) generally follow the standard approach for meta-analysis and systematic reviews as indicated by the original PRISMA statement (Mohler et al., 2009) including items such as aims, data sources, study selection, and sensitivity analyses. <u>However, in addition to not including the recent studies by Leijs et al., (2018), Donat-Vargas et al. (2017), Cao et al. (2019), and Magonia et al., (2018), each of these studies have some serious limitations, as indicated below.</u>

Overall, the peer reviewed articles, published since the IARC Working Group met in February 2013, support the conclusion in IARC (2016) that PCBs cause malignant melanoma in humans.

Critique of Boffetta et al. (2018) and Zani et al. (2017).

Overall, Boffetta et al., 2018 follow generally accepted methods for meta-analysis. However, they underestimate the risk presented in at least some of the positive studies and include in their meta-analysis at least some low-quality negative studies that should be excluded. Importantly, they do acknowledge in their final sentence that "results of internal analyses of selected studies are supportive of an association", and also acknowledge in their Conflict of Interest Statement that "Paolo Boffetta acted as expert in PCB-related litigation". Of note, the conflict of interest statement in Catalani et al. (2018) states that Paolo Boffetta (corresponding author for this publication) "consulted with Monsanto, a former PCB producer, on cancer risk from exposure to PCBs and other chemicals."

Specific concerns include the following:

- Boffetta et al. (2018) misinterpret the relative risk estimates for the retrospective occupational cohort study by Loomis et al., 1997. They cite a relative risk (RR) of 1.04, which apparently was taken from Table 1 in Loomis. This table, however, compares all electric utility workers in the study to men in the general US population. This is an inappropriate choice for at least two reasons: 1) not all the workers in the study were exposed to PCBs, and 2) comparisons of employed groups and the general population are biased due to the Health Worker Effect (HWE). The HWE is a well-known problem in occupational epidemiology (Checkoway et al., 2004) and is a result of the fact that healthy persons are more likely to gain and retain employment than is the general population, which includes those who are too ill or disabled to work. This is likely to attenuate the effects of occupational exposures compared to the general populations but is not addressed by Boffetta et al., 2018. Supporting this contention is that virtually all the results in Table 1 are suggestive of reduced mortality, a common feature of the HWE.

- A more valid estimate of the RR from Loomis et al., 1997 would be to utilize the internal estimates in Table 3, comparing those workers who were exposed to PCBs to those who were not exposed. A weighted average approach, utilizing RR values in Table 3, suggests that the RR of exposed to unexposed workers would be approximately 1.32. Assuming a 20-year latency, the RR increases to approximately 1.56. Given that Loomis et al.,1997 is among the largest studies, this change is RR estimates will significantly impact the results of the meta-analysis.

- A related concern is that latency is not well addressed in the Boffetta et al. 2018 review. This is a critical issue, since it typically takes decades for cancers to develop and it is the exposures that occurred prior to development that are biologically most relevant. Boffetta et al., 2018 do assess whether the studies included allow enough years of follow-up to permit cancers to develop. However, they do not consider whether the studies limited their

analyses to exposures that preceded the development of the cancer. One approach is to lag exposures, that is, to only include exposures that were 5, 10, or 20 years before diagnosis or death (Checkoway et al, 2004). In other words, if it takes 5, 10, or 20 years for a cancer to develop, then it is only exposures that occur before those time periods that caused the cancer. Loomis et al., 1996 do take latency into account with a lagged analysis and those analyses strengthen the findings, which supports a causal relationship. IARC, 2016 considers this an important feature of the Loomis et al. 1996 study, but it is ignored by Boffetta et al., 2018.

- Boffetta et al., 2018 also misrepresent the risk estimates for the Ruder et al., 2014 study. They cite a RR of 1.20 which apparently was taken from Table 3. However, this estimate compares all workers in the three capacitor plants to the general US population. As Ruder et al., 2014 note, almost one-third were short-term workers employed for less than three months. It is very unlikely that these workers would have incurred any meaningful exposure to PCBs in such a short time. A more appropriate comparison would be to use long-term workers who had a RR of 1.41.

- Another important finding in the Ruder et al., 2014 study is the observation that the RR for melanoma was significantly elevated in the Indiana (RR = 2.58) and New York (RR = 1.71) plants. In contrast, the RR for the Massachusetts plant was only 0.63. Ruder et al., 2014 note two possible explanations: 1) workers in the Massachusetts plant were more likely to have lower exposures (Table 1), and 2) they were more likely to be of Portuguese or Cape Verdean ethnicity with darker skin pigmentation, which is a protective factor for melanoma.

- Another study considered influential by IARC, 2016 is the Canadian case-control study of melanoma incidence and environmental PCB exposure by Gallagher et al, 2011. The key feature of this study was the direct measurement of PCBs in blood plasma, which helps to avoid misclassification of exposure. The results showed a strong dose- response association between melanoma incidence and plasma total PCB, with an odds ratio (OR) of 6.02 for the fourth (highest) quartile compared to the first (lowest quartile). However, Boffetta et al., 2018 use as their risk estimate the third quartile OR of 1.27, which is the quartile showing the lowest risk. A more appropriate choice would be a weighted average of all quartiles, which would be an OR of approximately 3.06.

- The quality analysis for each study investigated by Boffetta et al, 2018 was based on a modified version of the Newcastle–Ottawa Scale. This scale assigns a numerical value to whether the study meets certain criteria regarding design and analysis. Such an approach appears arbitrary in that it does not provide a rationale for its scoring and, based on the citations in the Boffetta et al., 2018, it does not appear to be peer reviewed. For example, the Czech study by Pavuk et al., 2004 has a total score of 10 in Table 1, which ranks it first along with Ruder et al., 2014. Pavuk et al. (2004) simply compares the rates of melanoma in each of two Czech districts to the general population with no information regarding the PCB exposure of the individual cases. Such a design suffers from ecologic bias, which as noted by the authors relates to the fact that "the implied association at the ecologic level (cancer patterns between the two districts with different PCB exposure levels) may or may not hold at the individual level". Epidemiologically this is considered a very weak design

(Morgenstern, 1995) but is not acknowledged by Boffetta et al, 2018. In fact, Pavuk et al. (2004) stated major limitations of their study, stating that, "this study must be interpreted with caution given the ecologic study design. Specifically, the implied association at the ecologic level (cancer patterns between the two districts with different PCB exposure levels) may or may not hold at the individual level, and may be due to other factors. We were also unable to control for confounding by lifestyle and other environmental factors."

- A more commonly accepted criteria for the quality of observational epidemiological studies is the STROBE report (Von Elm et al., 2014). Ideally, only those studies which meet this standard should be included in a meta-analysis. This would result in a smaller set of studies than those included by Boffetta et al, 2018, excluding at least some of those, such as Pavuk et al. (2004), which do not show an association between PCBs and melanoma.

In contrast to Boffetta et al. (2018), the systematic review and meta-analysis by Zani et al. (2017) showed a statistically significant overall risk of malignant melanoma with PCB exposure (pooled SMRs of 1.32, 95% CI: 1.05-1.64), despite underestimating the RR of melanoma with PCB exposure in Loomis et al., 1997. However, Zani et al. (2017) concludes that these findings do not provide a strong evidence that PCB exposure can increase the risk of melanoma based on arguments that the studies are biased or inconsistent. Their evaluation is not a balanced assessment of strengths and limitations but rather a systematic attempt to discredit and cast doubt upon the most positive studies. They report no conflicts of interest, but it very disconcerting that Zani et al. (2017) are from the same institution in Italy as is Bofetta (Department of Medicine and Surgery Specialties, Radiological Sciences and Public Health, University of Brescia, Italy). Specific concerns include the following:

- As with Bofetta et al., 2018, Zani et al., 2017 misinterpret the relative risk estimates for the retrospective occupational cohort study by Loomis et al.,1997. They cite a RR of 1.0, which apparently was rounded from the 1.04 value in Table 1 of Loomis. This table, however, compares all electric utility workers in the study to men in the general US population. This is an inappropriate choice for at least two reasons: 1) not all the workers in the study were exposed to PCBs, and 2) comparisons of employed groups and the general population are biased due to the Health Worker Effect (HWE).

- As with Bofetta et al., a more valid estimate of the RR from Loomis et al.,1997 would be the internal estimates comparing those workers who were exposed to PCBs to those who were not exposed, based on the results of Table 3. As stated above, a weighted average approach, utilizing RR values in Table 3, suggests that the RR of PCB exposed to unexposed workers would be approximately 1.32. Assuming a 20-year latency, the RR increases to approximately 1.56. Zanii et al., 2017 state on page 99 that subgroup analyses according to duration of employment, lag-time or cumulative exposure were not considered, but they give no rationale for this decision. This underestimate is important since Loomis et al., 1997 is among the largest studies and a change in the RR estimate will significantly impact the results of the meta-analysis.

- Although Zani et al., 2017 note that Loomis et al., 1997 found a dose-response relationship with cumulative exposure, they ignore the findings of the lagged analysis. This is a critical

issue, since it typically takes decades for cancers to develop and it is the exposures that occurred prior to development that are biologically most relevant.

- It is important to note that even with the underestimate of the RR for Loomis et al., 1997, the results of the meta-analysis show a statistically significant elevated risk for melanoma in the occupational studies (Figure 1). However, Zani et al., 2017 attempt to dismiss this association as invalid, citing possible biases and inconsistencies among the studies.

- For example, they acknowledge on page 113 that Loomis et al., 1997 and Tynes et al., 1994 found evidence of a dose-response relationship but then dismiss them because no such relationship was noted by Ruder et al., 2014. However, the lack of a dose-response relationship in Ruder et al., 2014, is likely driven by the fact that relatively few of the workers were heavily exposed. The majority worked for only 1 year or less, and only 14% were in the highest quartile for cumulative exposure (Table 2). As a result, there were too few cases in the highest exposure groups to adequately address the dose-response relationship.

- Similarly, Zani et al., 2017 acknowledge that the case-control study by Gallagher et al., 2011 of environmental exposure shows a dose-response relationship between plasma PCB levels and melanoma risk but then dismiss the study as biased. One argument is that the cases and controls were taken from two different parent studies. Although correct, this is unlikely to be a major problem because both were sampled from the same underlying population and the information was collected using the same methods. The controls were slightly older than the cases, but Gallagher et al., 2011 did adjust for age category in the statistical analysis. In addition, plasma PCB levels increase with age, which would tend to reduce the ORs.

- Zani et al., 2017 argue that the retrospective nature of the Gallagher et al., 2011 is a problem since the blood samples were collected after melanoma was diagnosed. This could result in "reverse causality", that is, the disease or treatment may have altered the plasma PCB levels of the cases relative to the controls. Gallagher et al., 2011 note this as a possible limitation (page 1879), since weight loss during chemotherapy may mobilize PCBs from adipose tissue. However, none of the patients received chemotherapy since localized surgery is the treatment of choice for melanoma.

- Zani et al., 2017 also claim that the analysis of the plasma for PCBs years after collection is a limitation. However, PCBs are very stable when frozen at - 80 C, and the plasma from 44 controls assayed in 2005 and again in 2008 showed substantially the same values. They also argue that contamination from storage in plastic containers is a concern, especially since the plasma for the cases was analyzed a few years later than that for the controls. It is true that some plasticizers may leach into plasma over time, interfering with PCB analysis, but this is not the case when glass containers are used. Gallagher et al., 2011 make no reference as to the type of containers used, so the contention that the PCB results were biased due to plastic containers is speculative at best.

- Zani et al., 2017 also argue against a causal association between PCBs and melanoma because of a lack of such a finding in the Yusho and Yu-Cheng studies in Japan and

Taiwan, respectively. It is correct that some participants in these studies were exposed to high levels of PCBs and suffered adverse health risks, although it is not clear whether these effects were due to PCBs or co-exposures to the more toxic PCDFs. They fail to note, however, that melanoma is rare among Asians, perhaps due to their darker skin type compared to Caucasians (Kim and Yun, 2016). Hence, they may be less predisposed to the development of melanoma than are the American and European populations in most of the other studies. Furthermore, although Li et al. (2015) reported a significant increase in all cancer deaths in male subjects from Yusho and Yu-Cheng, the total number of cancer deaths was less than 1/10th the number in the studies by Ruder et al. (2014) or Loomis et al. (1997), limiting the power to detect mortality due to melanoma, which is a relatively rare cancer.

c. Elevated risk of non-Hodgkin lymphoma (NHL) with general background, environmental PCB exposures

Rothman et al. (1997) investigated the association between risk of non-Hodgkin lymphoma (NHL) and serum PCBs in the general population in a nested case-control study. There was a strong dose-response relation between quartiles of total lipid-corrected serum PCB concentrations and risk of NHL overall (odds ratios by quartile: 1·3 [95% CI 0·5–3·3]; 2·8 [1·1–7·6]); and 4·5 [1·7–12·0]; p for trend=0·0008) and separately in men and in women. By contrast, total lipid-corrected serum concentrations of DDT were not associated with risk of NHL, supporting the specificity of the effect to PCBs.

Spinelli et al. (2007) investigated general background plasma levels of PCBs and risk of NHL in a large non-occupational, population-based case–control study in British Columbia, Canada. PCBs were measured in plasma of 422 cases (prior to cancer treatment) and 460 control subjects. The levels of total PCBs, sum of non-dioxin like PCBs and sum of dioxin like PCBs were all statistically associate with an increased odds ratio (OR) for all NHL, and for the subtypes of follicular and other B-cell NHL. For all NHL, the OR for total PCBs was 2.1 (CI, 1.4–3.3), for the sum of non-dioxin like PCBs 2.2 (CI, 1.4–3.4), and for the sum of dioxin like PCBs 2.4 (CI, 1.5–3.8). The results of this large study provide further evidence that general background levels of PCBs contribute to NHL risk and confirms the findings of earlier studies (De Roos et al., 2005; Rothman et al 1997; Hardell et al., 1996).

However, a recent nested case control study found no additional support for the previously observed role of PCBs, DDE and HCB as risk factors for NHL (Kelly et al., 2018). The authors suggest that the unexpected relationships may relate to the subtype composition of their population, effect modification by BMI or other unmeasured confounding.

Kramer et al. 2012 conducted a literature review to evaluate the epidemiological research examining the association between PCB exposure and Non-Hodgkin Lymphoma (NHL) and discuss the contribution to the weight of evidence of case–control studies and occupational cohort studies. They concluded that the weight of evidence supports a causal role of PCBs in NHL carcinogenesis, with the strongest evidence for this association coming from case–control studies conducted among the general population, including several prospective nested case–control studies. . Several case–control studies also provide evidence for biological interaction between blood levels of PCBs and titers of antibodies to Epstein-Barr virus early antigen (EBV-EA) and

risk of NHL, with elevated PCBs and antibody titers enhancing the risk of NHL (Hardell et al. 2009; Nordstrom et al. 2000; Rothman et al. 1997). Together, these studies indicate that PCB mediated immune dysregulation may represent a mechanism contributing to the increased risk of NHL.

The review by Kramer et al 2012 also discussed important methodological features of the occupational cohort studies. Generally, no direct measurement of PCBs in biological samples was used in analyzing disease risk associated with PCB exposure. Instead, exposure was estimated based on job titles, work history, or job-exposure matrices, possibly resulting in exposure misclassification. Additionally, because studies conducted in the past are typically limited to the older diagnostic criteria and outcome definitions available at the time of the study or at the time of the deaths, many occupational cohort studies examined only broad classifications such as "lymphatic and hematologic malignancies," and were not able to perform analyses specific to NHL. Studies with null findings for NHL were generally those that examined such larger outcome categories, not specific for NHL. In contrast, the studies that specifically examined NHL as a diagnosis or cause of death generally observed associations with PCB exposure (Gustavsson and Hogstedt 1997; Mallin et al. 2004; Prince et al. 2006a; Ruder et al. 2006). Comparisons of mortality in occupational cohorts to expectations for the general population may also be influenced by the healthy worker effect because employed populations generally have lower rates of disease than the general population, making any elevation in disease risk caused by occupational exposure more difficult to detect when using the general population as a comparison group (Rothman et al. 2008). Furthermore, most of the occupational cohort studies were underpowered to detect associations with NHL. Many focused on mortality, missing incident NHL cases that did not result in death. Studies that included incident cancer cases had few cases due to the relative rarity of lymphatic and hematologic malignancies, and specifically of NHL. Many of the workers in these studies were employed only for short durations and/or left employment at relatively young ages, thereby limiting the size of the at-risk population. An additional important factor contributing to the difficulty of comparing case-control and occupational cohort studies is the difference in the nature of the PCB mixtures in occupational settings versus environmentally bioaccumulated mixtures retained by participants in case-control studies.

Freeman and Kohles (2012) conducted a forensic epidemiologic evaluation of the causal relationship between NHL and elevated PCB levels via application of the Bradford-Hill criteria. "Included in the evaluation is a meta-analysis of the results of previously published case-control studies in order to assess the strength of association between NHL and PCBs, resulting in an odds ratio in which the lowest percentile PCB concentration (quartile, quintile, or tertile) has been compared with the highest percentile concentration in the study groups. The weight-adjusted odds ratio for all PCB congeners was 1.43 with a 95% confidence interval of 1.31 to 1.55, indicating a statistically significant causal association with NHL. Because of the lack of an unexposed comparison group, a rationale for the use of a less than 2.0 relative risk causal contribution threshold is presented herein, including an ecologic analysis of NHL incidence and PCB accumulation (as measured by sales volume) over time." The authors conclude that there is a strong general causal association between NHL and PCB exposure.

Zani et al. (2013b) conducted a systematic review and meta-analysis of scientific literature on the relationship between PCB exposure and human cancer. Several cohort and case-control studies investigated the association between PCBs and specific cancers, showing an association

between PCB serum levels and non-Hodgkin lymphomas (NHL), with a summary odds ratio of 1.5 (95% confidence interval: 1.1-1.7), but no consistent results for the other cancer sites and types. The association of NHL with individual PCB congeners found meta-analytical ORs ranging from 1.2 to 1.5 for some non-DL-PCBs with immune dysregulation activities, including PCBs 138, 153, and 180. Overall, the authors conclude that the studies provide some support to the hypothesis of a role of PCBs in NHL development, in agreement with the recent reviews of Freeman and Kohles 2012 and Kramer et al., 2012.

Zani et al. (2017) conducted another systematic review and meta-analysis of epidemiological studies on risk of non-Hodgkin lymphoma (NHL). Analysis of eleven independent cohort studies on occupationally exposed workers found a pooled SMR of 0.94 (0.73-1.23) for NHL. The authors also noted two cohort studies on people intoxicated by rice oil containing PCBs (Yusho and Yu-Cheng) which found inconsistent results for NHL. However deaths due specifically to NHL were not reported in Li et al. (2013) or the meta-analysis of these cohorts (Li et al., 2015). In contrast to occupational mortality studies, thirteen population-based cohort and case-control studies evaluated the association between NHL and PCB concentration in blood or subcutaneous fat, and reported a summary OR = 1.5 (1.1-1.7) for the highest vs lowest quantile of PCB distribution. This analysis supports a significant association between general background, environmental levels of PCBs and NHL.

In another recent review and meta-analysis of epidemiology studies, Catalani et al. (2018) concluded that PCBs are not likely to cause NHL in humans. A weak dose-response relation was detected in the meta-analysis of studies based on serum or fat PCB level in populations, with a meta-RR of 1.02 (95% CI: 1.00–1.04) for an increase of 100 ppb serum or fat PCB level. Of note, the conflict of interest statement in this publication states that Paolo Boffetta (corresponding author for this publication) consulted with Monsanto, a former PCB producer, on cancer risk from exposure to PCBs and other chemicals.

Weber et al. (2018) recently conducted a study of environmental PCB exposure and multiple myeloma in a population-based case-control study in British Columbia, Canada consisting of 325 cases of multiple myeloma and 327 controls. Significant associations were found between multiple myeloma and summed PCB level (highest vs. lowest quartile OR=1.87, 95% CI = 1.20 – 2.91, p trend = 0.0026), total dioxin-like summed PCB level (highest vs. lowest quartile OR=4.02, 95% CI = 2.36-6.85, p trend < 0.001), and total non-dioxin-like summed PCB level (highest vs. lowest quartile OR=1.98, 95% CI = 1.27-3.07, p trend < 0.001). This is the largest study to date to investigate the correlation between plasma PCB levels and multiple myeloma. However, the study was not able to identify any statistically significant differences between PCB level and multiple myeloma subtype. A major strength of this population-based case control study is the large number of participants with measured plasma PCBs at background levels of environmental exposure. In addition, the investigators showed that this relationship was not affected by excluding cases with substantive weight loss or chemotherapy prior to sample collection, which are factors that may alter plasma PCB levels.

Klil-Drori et al. (2018) also recently compared serum levels of 38 PCBs in Israeli Jews (IJ) and Palestinian Arabs (PA) and assessed possible associations with B-cell non-Hodgkin lymphoma (B-NHL). Ninety B-NHL cases (50 IJ and 40 PA) and 120 controls (65 IJ and 55 PA) were included. Logistic regression was used to derive odds ratios (OR) and 95% confidence

intervals (CI) for detectable analytes and B-NHL, adjusting for age, ethnic group, faming and body mass index. B-NHL was associated with PCB 146 (OR 1.70, 95% CI: 1.02, 2.83), PCB 156 (OR 1.75, 95% CI: 1.06, 2.89), and high-chlorinated PCBs (sum of 138, 146, 153, 156, 163, 170, 180, 183 and 187) (OR 1.55, 95% CI: 1.00, 2.40) in all study subjects. These associations were also robust in quantile analyses for the highest quartile of exposure for PCB 138 (OR 2.87, 95% CI: 1.11, 7.38; p for trend 0.02) and PCB 153 (OR 3.24, 95% CI: 1.19, 8.86; p for trend 0.03). Although PCB concentrations did not indicate high exposure levels, our findings indicate that B-NHL may be associated with this exposure. Thus, case control studies of the general population with background, environmental PCB exposures show that PCBs cause an increase in multiple myeloma and NHL, which are related malignancies in that they both involve white blood cells.

Together, the above studies provide support for the conclusion that background, environmental PCB exposures cause an increase in the risk of NHL.

d. Elevated risk of breast cancer with general background, environmental PCB exposures

Parada et al. (2016) investigated background, environmental levels of PCBs in serum at the time of diagnosis of breast cancer and their association with survival following diagnosis. The highest PCB174 tertile was associated with an increase in all-cause (HR=2.22, 95% CI: 1.14–4.30) and breast cancer-specific (HR=3.15, 95% CI: 1.23–8.09) mortalities within 5 years of diagnosis. The elevated hazard ratio (HR) remained associated with breast cancer-specific mortality (HR=1.88, 95% CI: 1.05–3.36) at 15 years. At 5 years, the highest tertile of PCB177 was positively associated with all-cause mortality (HR=2.12, 95% CI: 1.05–4.30). At 15 years, the highest tertiles of ΣGroup 2A anti-estrogenic congeners PCB66, PCB74, PCB105, and PCB118 and PCB118 were inversely associated with all-cause mortality (HR=0.60, 95% CI: 0.39–0.83; HR=0.63, 95% CI: 0.43–0.92, respectively). In this first US study of PCBs and breast cancer survival, PCBs were associated with mortality in biologically plausible directions, with estrogenic PCBs 174 and 177 increasing breast cancer-specific mortality and all-cause mortalities.

He et al. (2017) investigated the association between breast adipose PCB exposure in breast cancer patients and breast cancer development, which can provide clues for exploring the contribution of PCBs to human breast cancer. With increased clinical stage, the level of sum or total PCBs increased significantly. The level of total PCB did not differ by tumor–node–metastasis classification and PR or human epidermal growth factor receptor 2 (HER2) expression but did differ by estrogen receptor (ER) expression (higher PCBs in ER+ cases) (P = 0.04) without a regularly increasing trend in breast adipose tissue. These results suggest a potential association between PCB exposure and breast cancer development.

Zhang et al. (2015) conducted a meta-analysis of 25 breast cancer studies, involving a total of 12866 participants (6088 cases and 6778 controls) from eight countries. Studies were included for statistical analyses if they fulfilled the following criteria: to be observational studies (case-control or cohort studies); to have measured PCB levels in biological samples (adipose tissue, serum or plasma); to have reported measures of association (odds ratio, relative ratio) and 95% confidence intervals (95% CIs) for breast cancer risk. The results showed that the risk of breast cancer was associated with group II (OR = 1.23, 95% CI: 1.08–1.40) and group III (OR = 1.25, 95% CI: 1.09–1.43) PCBs, but not with group I (OR = 1.10, 95%CI: 0.97–1.24) PCBs or total PCB exposure (OR = 1.09, 95%CI: 0.97–1.22). The results of the meta-analysis found that group II

(potentially anti-estrogenic and immunotoxic, dioxin-like) and group III (phenobarbital, CYP1A and CYP2B inducers, biologically persistent) PCB exposure contributed to the risk of breast cancer. It is important to note that the meta-analysis is directly relevant to cancer risk associate with background, environmental PCB exposures and that the analysis did not include occupationally exposed female workers.

Recently, a hospital-based case-control study of 209 newly diagnosed breast cancer cases and 165 controls assessed the associations between adipose tissue PCB, DDT, and DDE levels and breast cancer risk (Huang et al., 2019). Multivariate logistic regression models adjusted for age, menarche age, ever breastfeeding, and menopausal status found that PCB-118, 138, PCB 153, 180, the sum of seven PCB congeners, and p,p′-DDE were significantly higher in adipose tissue of participants with breast cancer, suggesting that PCB exposures increase breast cancer risk.

Leng et al. (2016) conducted a quantitative meta-analysis of the effects of specific PCB congeners on breast cancer. The pooled Odds Ratios (ORs) showed a significant increase in the risk of breast cancer in individuals with higher plasma/ fat levels of PCB 99 (OR: 1.36; 95% CI: 1.02 to 1.80), PCB 183 (OR: 1.56; 95% CI: 1.25 to 1.95) and PCB 187 (OR: 1.18; 95% CI: 1.01 to 1.39), while no increase in risk was found for dioxin-like PCBs. The authors concluded that the mechanism of this effect might be through the induction of the CYP2B family of cytochrome P450 enzymes. The authors also addressed the issue of multiple comparisons where as the number of tests increases, so does the probability that the findings are statistically significant just by chance. Since breast cancer was the only end point in the sixteen studies included this the meta-analysis, correcting for multiplicity had been avoided in the original studies as well as in the meta-analysis which found that PCB 99, PCB 183 and PCB 187 are associated with an increase in the risk of breast cancer (Leng et al., 2016). These findings are consistent with that reported in the meta-analysis by Zhang et al. (2015), where PCBs 99, 183 and 187 are biologically persistent CYP2B inducers which contributed to the risk of breast cancer.

The meta-analyses of Zhang et al. (2015) and Leng et al. (2016) provide further support for an association between PCB exposure and increased risk of breast cancer.

e. Elevated risk of gastrointestinal cancer with occupational and general background environmental PCB exposures

In a case-control study in the general population with background, environmental PCB exposures, Howsam et al. (2004) reported an elevated risk of colorectal cancer was associated with higher serum concentrations of mono-ortho PCB congeners 28 and 118. The odds ratio for these mono-ortho PCBs for middle and higher tertile were, respectively, 1.82 [95% confidence interval (CI), 0.90–3.70] and 2.94 (95% CI, 1.39–6.20). Risk associated with mono-ortho PCBs was slightly higher for tumors with mutations in the p53 gene but was not modified by mutations in K-ras. Mono-ortho PCBs were further associated with transversion-type mutations in both genes. The authors conclude that these results support the hypothesis that exposure to mono-ortho PCBs contributes to human colorectal cancer development. The trend and magnitude of the association, as well as the observation of a molecular fingerprint in tumors, raise the possibility that this finding may be causal. Additional support for this association comes from the occupational mortality

study of PCB capacitor workers from New York (Kimbrough et al. 2015). Carcinoma of the rectum was statistically significantly increased in the combined cohort (SMR 167; CI 107–249; p\0.05), but not separately among males or females. Among women, intestinal cancer mortality was elevated (67 deaths; SMR 1.31; 95% CI, 1.02–1.66), especially in higher cumulative exposure categories (Prince et al., 2006 b). Ruder et al. (2014) also found evidence of associations between employment in capacitor manufacturing and increased total cancer and intestinal cancer mortality among female long-term workers.

f. Elevated risk of prostate cancer with occupational and general background environmental PCB exposures

While earlier studies assessing the association between biomarkers of PCB exposure and prostate cancer risk in the general non-occupationally exposed population show inconsistent findings, the results from the most recent case-control studies show consistent positive associations of PCB exposure and risk of prostate cancer. Based on 58 cases and only 20 controls, the concentrations of the non-dioxin-like PCB153 in abdominal fat were associated with significantly increased odds of higher prostate-specific antigen concentrations (>16.5 ng/ml) at diagnosis of prostate cancer as compared with those with lower levels and controls (Hardell et al., 2006). Similarly, higher serum levels of nondioxin- like PCBs (including PCB153) were associated with higher odds of prostate cancer based on 58 cases with moderately or poorly differentiated tumors (Ritchie et al., 2005). However, a study by Aronson et al. (2010) suggests that long-term low-level exposure to organochlorine pesticides and PCBs in the general population does not contribute to increased prostate cancer risk. Similarly, no increased risk was observed for advanced prostate cancer (extra prostatic or metastatic cancer or Gleason score 8–10) based on the sum or on individual serum PCBs in 201 prospective cases from Japan (Sawada et al., 2010). Based on 576 cases of prostate cancer in men from the French West Indies, tertiles of serum PCB153 were inversely associated with odds of low-grade prostate cancer (Gleason <7 and 3+4), whereas no association was observed for the 101 cases with high-grade score (Gleason >7 and 4+3) (Emeville, et al., 2015).

Hardell et al. (2006) studied the adipose tissue concentrations of PCBs in cases with prostate cancer and controls with benign prostate hyperplasia. A greater-than median concentration of PCB congener 153 in the controls yielded an odds ratio (OR) of 3.15 and 95% confidence interval (CI) of 1.04–9.54. In the group of case subjects with PSA levels greater than the median level of 16.5 ng/mL, PCB 153 was OR 30.3 (95% CI_3.24–284). In cases with PSA levels greater than 10 ng/mL, the OR for PCB 153 was 7.91 (2.00 –31.2) The grouping of PCBs according to structural and biological activity was found to produce significantly increased risks for enzyme and phenobarbital-inducing PCBs and lower chlorinated PCBs in the case group with PSA levels greater than 16.5 ng/mL. The authors concluded that PCB153 might be of etiologic significance but need to be investigated further.

Lim et al (2017) used prospective cohort data to conduct a case-cohort study to evaluate the association between serum concentrations of PCBs and the risk of prostate cancer incidence in a Korean population. Compared to the lowest tertile, increased risks of prostate cancer incidence were observed in the upper tertile of moderately chlorinated PCBs (Hazard Ratio, HR: 4.19; 95% CI: 1.30–13.54), the highly chlorinated PCBs (HR: 4.14; 95% CI: 1.75–9.79), biologically persistent as CYP1A and CYP2B inducers (HR: 4.44; 95% CI: 1.33–14.83), the sum of non-

dioxin-like PCBs (HR: 3.47; 95% CI: 1.21–9.98), and _PCBs (HR: 4.29;95% CI: 1.52–12.08). In dose-response curves, _PCBs were associated with the increased risk of prostate cancer.

In a case-control study of stage 1 prostate cancer, mean concentrations of PCB118, PCB138, PCB153 and PCB187 were significantly higher (p<0.05) in serum of patients (Pi et al., 2016). The results suggest that exposure to PCBs may be associated with prostate cancer risk in Singaporean males.

Ali et al (2016) identified a population-based cohort of 32,496 Swedish men aged 45–79 years was followed prospectively through 1998–2011, to assess the association between validated estimates of dietary PCB exposure and incidence of prostate cancer by grade (2789 cases, with 1276 low grade, 756 intermediate grade, 450 high grade) and prostate cancer mortality (357 fatal cases). After multivariable-adjustment, dietary PCB exposure was positively associated with high-grade prostate cancer, relative risk (RR) 1.35 [95% confidence interval (CI): 1.03–1.76] and with fatal prostate cancer, RR 1.43 (95% CI: 1.05–1.95), comparing the highest tertile with the lowest. No association with low or intermediate grade of prostate cancer. The major strengths of this epidemiological study is that it was population-based with a prospective study design, which eliminates recall and selection bias. In addition, they investigated a non-dioxin-like PCB153-induced cell invasion and related markers in normal prostate stem cells (WPE-stem) and in three different prostate cancer cell lines (PC3, DU145 and 22RV1) at exposure levels relevant to humans (10nM). Cell invasion and related markers, including MMP9, MMP2, Slug and Snail, were significantly increased in human prostate cancer cells as well as in prostate stem cells after exposure to PCB153. These experimental results support the findings of the observational epidemiological study. The findings both from the observational and experimental studies suggest a role of non-dioxin-like PCB153 in the development of high-grade and fatal prostate cancer.

Results from these case-control studies are supported by occupational studies reporting higher prostate cancer mortality at high cumulative PCB exposure in occupationally exposed electrical capacitor manufacturing workers (Ruder et al. 2014; Prince et al. 2006). The study by Prince et al. (2006b) was the first occupational cohort study showing a strong exposure–response relationship between cumulative PCB exposure and mortality from prostate cancer.

g. Elevated risk of thyroid cancer with background environmental PCB exposure

Lerro et al. (2018) conducted a nested case-control study of thyroid cancer in the Norwegian Janus Serum Bank cohort using pre-diagnostic blood samples from 1972 to 1985. Incident thyroid cancer (n=108) was ascertained through 2008. Controls were matched 2:1 by age, date of blood draw, gender, and county. Among participants in the youngest birth cohort (1943–1957), we observed positive associations with thyroid cancer for total PCBs and the sum of the moderately chlorinated PCBs including 138/158 and 153, suggest that early-life exposure contributes to cancer risk.

Together, the above studies of occupational PCB exposures and background, environmental PCB exposures in the general population support the designation of PCBs as know human carcinogens.

IV. CONCLUSIONS

In summary, PCBs pose a significant threat to human health due to their wide-spread use, persistence, and inherent toxicity. It is clear from the published scientific literature, as early as the 1930s, that PCBs produce systemic toxicity in humans and in laboratory animals.

An extensive body of peer reviewed scientific studies, including those of ATSDR 2000, 2011; EPA 1985, 1989, 1996a, 1996b, 2018; IARC 2016, support the conclusion that PCBs cause an increased risk of a number of adverse health effects, including cancer, developmental effects, diabetes, liver injury, immune system dysfunction, neurobehavioral effects, impaired thyroid function, reproductive system impairment, cardiovascular disease, and chloracne. These adverse health effects are observed in association with PCB exposures in the general population, at background, environmental levels of exposure to PCBs. Thus, an increase in human exposure to PCBs results in an increased risk of developing cancer and other adverse health effects. In addition, PCB exposure to children, women of childbearing age, and pregnant women is especially dangerous due to PCBs adverse developmental effects. Therefore, efforts should continue to reduce human exposures to PCBs, which will in turn reduce health risks due to these persistent environmental contaminants.

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